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# MULTIPLE DEGENERATIVE SOFTENING

## CLINICOPATHOLOGIC REPORT OF THREE CASES

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There are a number of diseases of the central nervous system in which even typical clinical manifestations, such as hemiplegia or paraplegia, cannot adequately be interpreted by the established etiologic factors—infection, trauma, neoplasms or vascular disturbances. Intoxication, popularly accepted as an etiologic agent in some disturbances of peripheral nerves, is, with the exception of that due to lead, seldom considered at the bedside as the cause of a disease of the brain or the spinal cord. Yet toxic factors, intoxications, undoubtedly cause acute or subacute nervous disorders, which always exhibit definite histopathologic features but only occasionally possess a suggestive clinical picture. For this reason many disorders of the central nervous system remain undiagnosed and consequently improperly treated. The histopathologic features in cases of such disturbances are typical of what has been described [1] as multiple degenerative softening, which is a combination of parenchymatous and inflammatory changes; their clinical features may resemble those of any inflammatory, degenerative, vascular or neoplastic disease process. Of a number of such cases observed, 3 will be recorded in some detail.

### REPORT OF CASES

CASE 1.—*Brown-Séquard syndrome. Clinical diagnosis: tumor of the spinal cord; pathologic diagnosis: multiple degenerative softening.*

*History.*—A white man aged 28 was admitted to the Research and Educational Hospital on Jan. 11, 1939, because of "coldness" of the right side of the body and

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1. (*a*) Hassin, G. B., and Bassoe, P.: Multiple Degenerative Softening Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:613 (May) 1922. (*b*) Hassin, G. B.: Neuroptic Myelitis Versus Multiple Sclerosis, ibid. **37**:1083 (May) 1937; (*c*) Pathologic Features of Multiple Sclerosis and Allied Conditions, ibid. **38**:713 (Oct.) 1937.

paralysis and numbness of the left side, the numbness involving also the left side of the face and tongue.

On Nov. 20, 1938 the patient had an acute febrile state (with a temperature of 102 F.), which was diagnosed as influenza. He recovered within five days, but three weeks later (December 18) he commenced to experience a feeling of coldness and numbness in the thumb of the left hand. The numbness, during the following three days, extended to the rest of the fingers of the left hand and from there to the entire left upper extremity. The left leg and arm were growing weak, and pain set in in the left pectoral muscle and radiated to the costal margin and down the left arm and fingers. The patient also experienced paresthesias in the left side of the tongue, and the cold feeling spread to the left side of the face (from the lower angle it was gradually extending upward until it reached about the level of the ear). The symptoms progressed, and complete paralysis of the left upper and lower extremities developed, associated with a complete numbness of the left side of the body and coldness of the right side. Difficulties in starting the urinary stream and emptying the bladder set in a few days later (January 11). He complained of much pain in the left side of the body, especially on sudden movements and in the morning hours. Since December 20 there had been slight difficulty in speaking and swallowing, which was due most likely to the numbness of the tongue and face. These difficulties soon disappeared.

*Neurologic Examination.*—On the left side there were hemiplegia with exaggerated tendon reflexes, Babinski, Rossolimo and Oppenheim signs and loss of abdominal and cremasteric reflexes; loss of the senses of position, vibration, touch and temperature to and just above the clavicle, and atrophy (without fibrillary twitchings) of the trapezius muscle and the arm. On the right side there was loss of the senses of pain and temperature below the clavicle. The corneal and pharyngeal reflexes were present, and the pupillary reactions were normal.

*Laboratory Examination.*—The blood contained 78 per cent hemoglobin, 5,100,000 red cells and 15,100 white cells per cubic millimeter.

The spinal fluid was clear and colorless; it contained 2 to 3 cells per cubic millimeter. The initial pressure was 110 mm.; an instantaneous touch caused a rise to 140 mm., with a return to 110 mm. On deep jugular compression the pressure was 200 mm., with a return to 120 mm. After withdrawal of 7 cc. of spinal fluid the pressure was 80 mm., and on deep compression it rose to 170 mm., with a return to 70 mm. The Pandy reaction was negative; the total protein content was 53 mg. per hundred cubic centimeters.

The skull and the cervical portion of the spine exhibited no abnormalities.

*Diagnosis.*—The diagnosis was tumor of the spinal cord.

*Operation.*—A cervical laminectomy (first to fourth cervical vertebrae, inclusive), performed by Dr. Eric Oldberg on Jan. 21, 1939, was reported on as follows:

"The subarachnoid space was almost obliterated by a thick, turgid cord, which had every evidence of harboring a rapidly growing intramedullary lesion. I therefore punctured the dense pia in the left anterior quadrant with a pair of forceps, and immediately pale, softened material began herniating from the small rent in the pia. This material could be picked up with a curet and was not fibrous and stringy, like normal cord tissue. I felt, therefore, that it must represent a glioma or some other infiltrating lesion of the cord, such as lymphoma. . . . I desisted from further manipulation, since the patient's respiration increased considerably at this point . . ."

Microscopic examination of the tissue taken for biopsy revealed numerous compound fat corpuscles, blood vessels infiltrated with lymphocytes and compound fat corpuscles and fibrillary and cytoplasmic astrocytes. The diagnosis was myelomalacia.

Fig. 1 (case 1).—Demyelination of the third and fourth cervical segments (upper two sections). In the fourth cervical segment the demyelination is in the form of a crescent; in the third the demyelination left only a small part intact. The lower two segments (eighth cervical and second lumbar) exhibit no signs of secondary degeneration. Weil stain.

The patient died the following day.

*Gross Pathologic Observations* (Dr. W. O. Brown).—The dura was smooth and glistening and stripped easily from the skull. The brain weighed 1,340 Gm., and its cortical blood vessels were congested. The basilar arteries were normal. There had been recent resection of the dorsal laminas of the first four cervical vertebrae. The soft tissues in this region were softened and hemorrhagic.

*Microscopic Observations.*—The upper five cervical segments of the spinal cord exhibited extensive demyelination (fig. 1), which appeared as a crescent in the fifth segment, where it occupied a part of the posterior columns and the entire left posterior horn. The third cervical segment was almost totally demyelinated, only a small fragment of the white matter remaining intact (fig. 1). In sections stained with hematoxylin and eosin, toluidine blue and similar stains the demye-

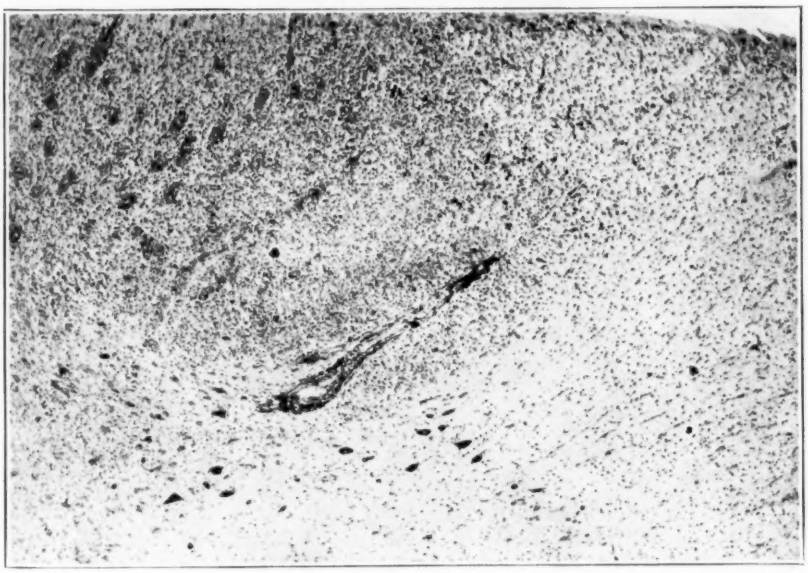

Fig. 2 (case 1).—Excessive cellularity and extensive perivascular infiltration of the demyelinated area. The vascular lumens are patent even in the densely infiltrated blood vessels. Toluidine blue stain.

linated areas appeared extremely cellular (fig. 2). The cells were practically all gitter cells (compound fat corpuscles); their vacuoles varied in size and their nuclei were eccentric, polymorphous and rich in chromatin. Mixed with these elements were rodlike cells which possessed numerous ramifying delicate processes, and it was possible to trace their transformation into the previously mentioned compound fat corpuscles, which thus were largely of microglial origin. The assertion by Bassoe and Grinker [2a] with respect to Hassin's "objection to the conception of the origin of gitter cells from microglia, which he advanced because microglia have not been demonstrated in pathologic processes within the spinal

2. (*a*) Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. **23:** 1138 (June) 1930. (*b*) Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis: Its Relation to Other Infections of the Nervous System, ibid. **25:**723 (April) 1931.

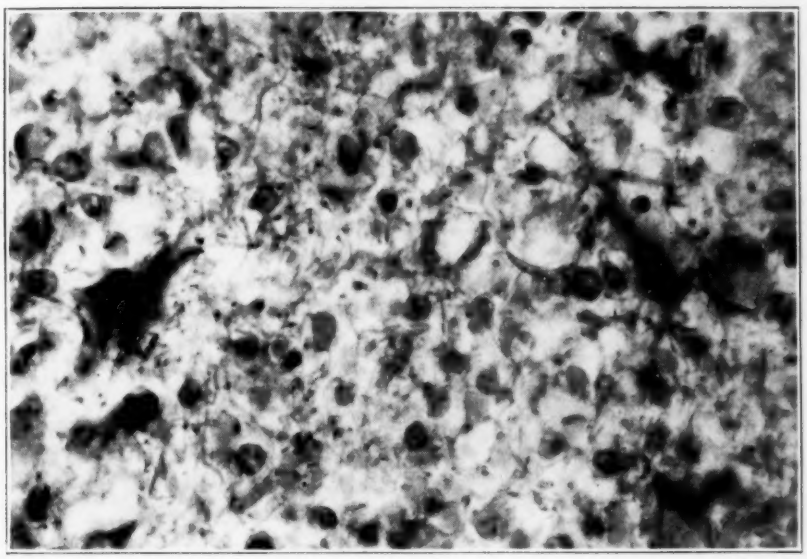

Fig. 3 (case 1).—Cytoplasmic astrocytes in a demyelinated area; an astrocyte to the left contains two nuclei. Holzer stain.

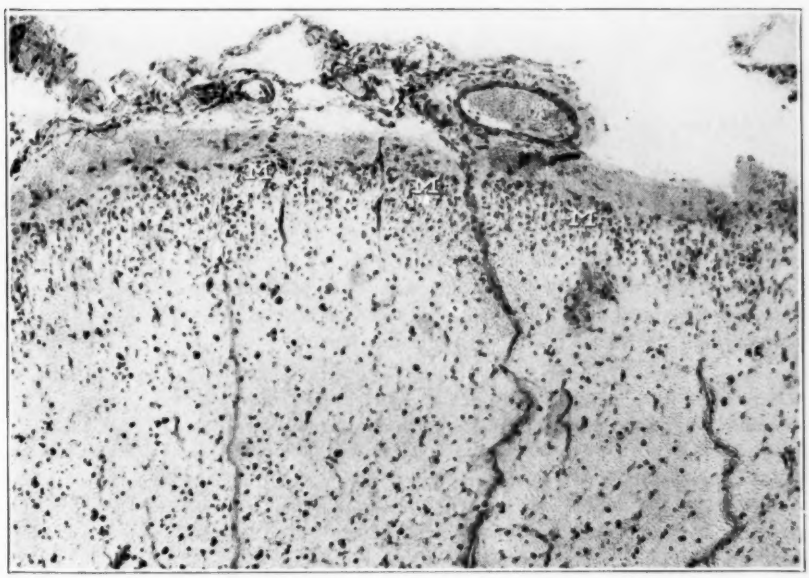

Fig. 4 (case 1).—Sacral region of the spinal cord. The marginal glia is lined by rows of microglia cells (*M*), which are numerous also over the parenchyma below. The meninges and the blood vessels are patent and infiltrated. Toluidine blue stain.

cord" is not wholly correct. I (Hassin) denied, and still deny, the occurrence of microglia in a nonpathologic spinal cord, but in a pathologic spinal cord microglia tissue is common, when, of course, it may give origin to gitter cells. In some demyelinated areas astrocytes were present, some of which were of huge size (fig. 3), contained several nuclei and were intermingled with masses of microglia cells, mainly along the marginal areas of the spinal cord (fig. 4). Oligodendrocytes were not in evidence, either in the demyelinated or in the adjacent healthy areas. The blood vessels showed dilatation of their adventitial spaces and dense infiltration with lymphocytes and gitter cells. Regardless of the severity of the infiltrations, the vascular lumens were always patent (figs. 2 and 8). In the smaller blood vessels and capillaries the endothelial and adventitial cells stained brightly, and their nuclei were often large and rich in chromatin. No

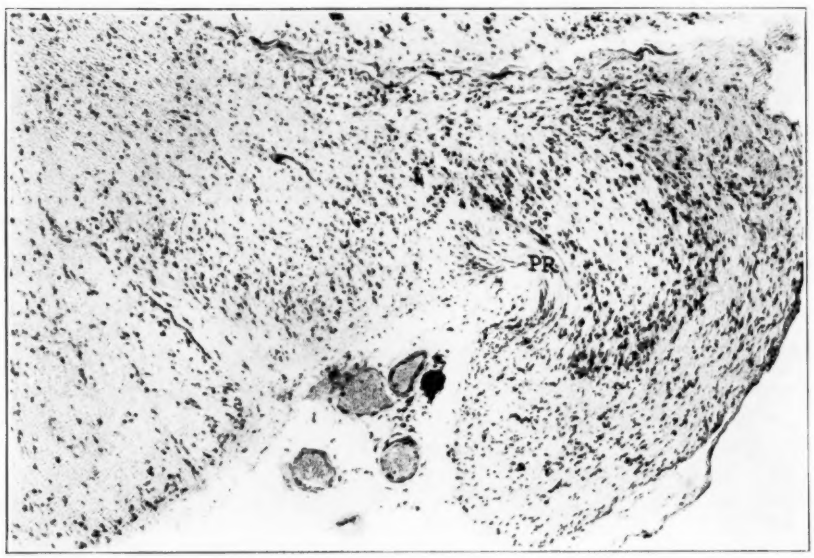


Fig. 5 (case 1).—Focus of microglia cells at the entrance of the posterior root into the spinal cord. The microglia cells are numerous over the parenchyma of the spinal cord. *PR* indicates some of the posterior root fibers at their entrance into the spinal cord. Van Gieson stain.

nerve fibers were detected (Bielschowsky's method) in the demyelinated areas, and the occasional few axons scattered among them were somewhat tumefied.

The ganglion cells were swollen; some appeared homogeneous and occasionally were liquefied.

Noteworthy changes were present also in the posterior roots. Their degenerated central portions (fig. 5) contained many microglia cells and were covered caplike by bundles of normal nerve fibers, which extended into the spinal cord (especially well seen at *PR*). Similar, though less striking, changes were present also in the anterior roots.

The areas that bordered on those of demyelination exhibited under a high power lens masses of microgliocytes, especially in the marginal areas of the spinal cord, which were usually mixed with fibrillary and cytoplasmic astrocytes. Both types of cells, especially the microglial, were present throughout the spinal cord,

even as far as the sacral region; they were present also in the medulla, pons, midbrain, optic thalamus and cerebellum, but were scarce in the cortical areas. No proliferation of connective tissue was in evidence. Astrocytes were present in both the gray and the white substance of both the affected and the unaffected areas. They were for the most part fibrillary and were mixed with the microglia cells and other elements described previously. The spinal meninges were at some levels densely infiltrated (fig. 6) with lymphocytes, polyblasts, gitter cells and occasionally polymorphonuclears.

Above and below the demyelinated region the spinal cord, as figure 1 shows, exhibited no changes in the nerve fibers.

The marked involvement of the upper cervical segments, including the posterior cornua and Rolando's gelatinous substance, which is the end station of the descending fibers of the fifth nerve, accounts for the paresthesias of the face and

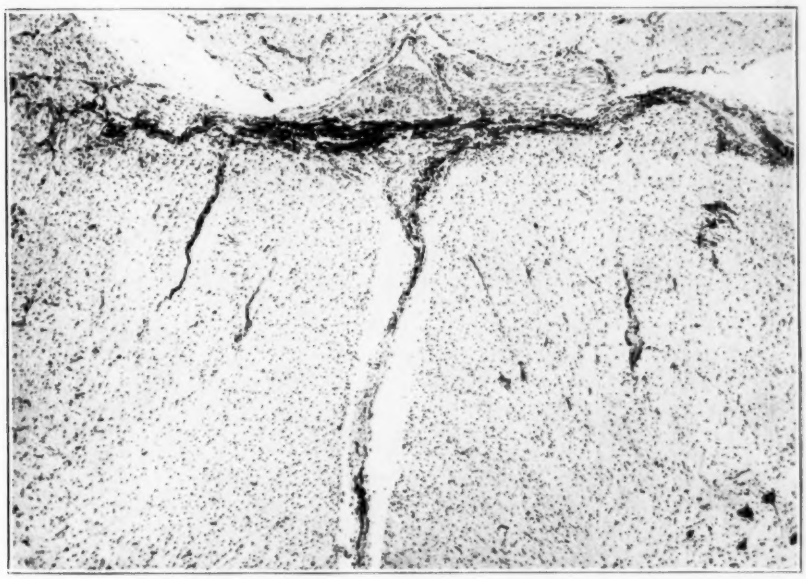

Fig. 6 (case 1).—Infiltration of the spinal meninges and their prolongations, described in the text. Toluidine blue stain.

tongue, while the almost total demyelination of some segments may explain the bilateral disturbance of other forms of sensibility.

Summary: The histologic changes were extensive demyelination of the upper segments of the cervical portion of the cord, combined with inflammatory and meningeal changes and extensive microglial and less extensive neuroglial reaction throughout the spinal cord, medulla, pons and midbrain. The dominant pathologic feature was degeneration combined with inflammation.

CASE 2.—*Hemiparesis four months after systemic infection (influenza and pneumonia); three months later a remission (of four months) followed by exacerbation; another remission and short exacerbation, with death from respiratory paralysis. Necropsy: multiple degenerative softening of the upper cervical region and the medulla.*

A white woman aged 21 was admitted to the Cook County Hospital (service of Dr. T. T. Stone) on Jan. 15, 1939 because of difficulty in walking and adiposity.

*History.*—In November 1936 the patient had had an infectious disease which was diagnosed as influenza and pneumonia. Two months later she complained of visual disturbances and drowsiness; her temperature became elevated, and the right half of the body, including the lower portion of the face, became paralyzed and somewhat rigid. The tendon reflexes were exaggerated; the tongue was coarsely tremulous, and speech was slow and hesitant. The pupils were small, round and equal and reacted poorly to light and in accommodation.

Fig. 7 (case 2).—The upper dorsal segment of the spinal cord, containing foci of demyelination. Weil stain.

The spinal fluid was clear and under a pressure of 15 mm. of water; there was no evidence of a block. The Ross-Jones test gave a positive reaction. There were 36 lymphocytes per cubic millimeter and 55 mg. of protein per hundred cubic centimeters. The Wassermann reactions of the blood and the spinal fluid were negative, and the Lange colloidal gold curve was represented by a straight line.

The patient recovered after six intravenous injections of typhoid vaccine and was discharged in June 1937. During the four months following the recovery she gained 60 pounds (27.2 Kg.) in weight but was otherwise apparently well. In October she experienced increasing difficulty in walking, which disappeared in a short time but recurred in December 1938. On Jan. 2, 1939 the right leg

became numb and weaker; the patient had hiccup, vomited and became paralyzed on Jan. 9, 1939.

*Examination* (Jan. 15, 1939).—The patient was obese and drowsy; there were absence of movements of the toes of the right foot and "questionable" paralysis of the lower extremities; the left knee and ankle reflexes were exaggerated, with a suggestive Babinski sign bilaterally and ataxia in "the left index finger" while performing the finger to nose test; the Pandy reaction was positive. On Feb. 5, 1939 there was paresis of the left upper extremity and respiratory disturbances set in, followed by death on February 6.

*Diagnosis.*—The anatomic diagnosis was acute encephalitis; focal bronchopneumonia in the lower lobes of both lungs; hemorrhagic infarct in the lower lobe of the right lung; parenchymatous degeneration of the heart; infectious

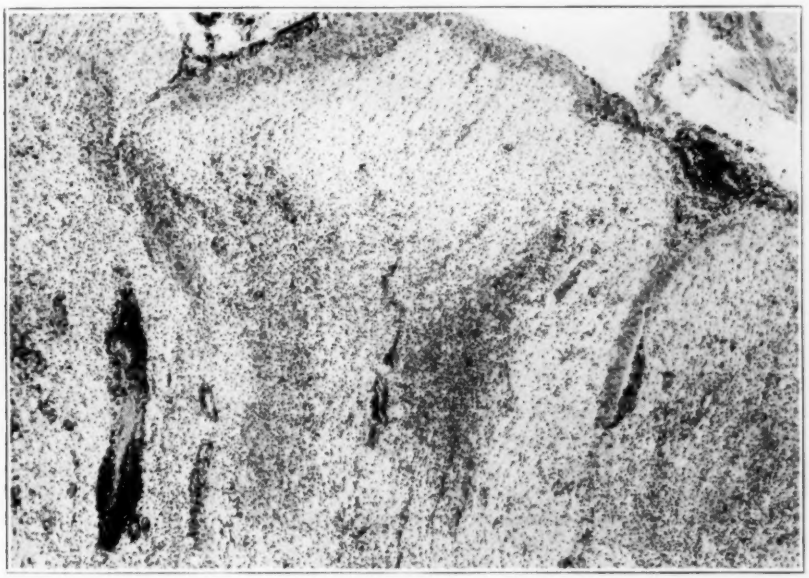

Fig. 8 (case 2).—Cellularity and perivascular infiltrations of the posterior columns of the spinal cord. The blood vessels are patent. Toluidine blue stain.

hyperplasia of the spleen; pyelitis; passive congestion and fatty changes of the liver, and aberrant spleen.

*Gross Pathologic Observations.*—The meninges were normal; the pial veins were engorged, and the large blood vessels of the base of the brain were soft and patent; the spinal cord exhibited grossly nothing pathologic.

*Microscopic Observations.*—The microscopic changes, similar to those described in the previous case, were degenerative and inflammatory. The degenerative changes appeared as foci of demyelination in the thoracic region of the spinal cord (fig. 7). These consisted of masses of microglial fat granule bodies mixed with fibrillary and numerous cytoplasmic astrocytes and microgliocytes, gathered in large masses at the periphery of the spinal cord, and occasional plasma cells (free in the softened tissues); enormous cufflike (fig. 8) infiltrations (with lymphocytes, plasma cells and gitter cells) of the blood vessels, mainly of the white substance, and swelling of the ganglion cells of the gray matter with

phenomena of neuronophagia and satellitosis and numerous microglia cells in the field. There was absence of secondary degeneration above or below the areas of softening, of changes in the endothelial or adventitial tunics and of thrombi formation.

Inflammatory changes were marked also in the medulla, pons and subependymal areas of the optic thalamus, which were rich in microglia cells. In the cortex and subcortex these were rare. The meninges at the base and over the convexity of the brain were infiltrated with lymphocytes, fat granule bodies and polyblasts. On the whole, the inflammatory changes were more in evidence than the degenerative. Both were local, while the reactive microglial changes were diffuse, extending, as in the previous case, throughout the normal-appearing portions of the brain and spinal cord. The hypothalamus, optic tract and optic nerves were not studied, as they had been removed before the brain was delivered to the laboratory.

CASE 3.—*Injury to the occiput ten years previously; aching pain in the occipital region of four months' duration, which followed extraction of several teeth and preceded sudden fainting and death. Necropsy: subdural hemorrhage and a focus of degenerative softening in the medulla.*

A farmer aged 38 was brought to the Research and Educational Hospital on Jan. 25, 1939 in a semicomatose condition.

*History.*—In 1929 the patient was struck in the suboccipital region but did not become unconscious. In September 1938 he had three teeth extracted and after this began to experience a dull, aching pain in the suboccipital region. The pain grew steadily worse and incapacitated him. On June 21, 1939 he fainted on the street, vomited four times and became drowsy. There were no convulsions, biting of the tongue or loss of sphincter control.

*Examination.*—The patient was semistuporous and incontinent and responded to painful stimulations; the tongue was parched, and the teeth were covered with a dirty film; there was some rigidity of the neck. The cranial nerves and the reflexes were normal; there were no atrophies or muscular fibrillations. A small amount of serosanguineous fluid was obtained by cisternal and spinal punctures. Roentgen examination (anteroposterior, posteroanterior and lateral exposures) revealed a small radiolucent area in the right parietal region, of doubtful significance.

*Laboratory Examination.*—The urine contained no albumin, casts or sugar. Examination of the blood revealed 90 per cent hemoglobin; 6,100,000 red cells and 11,800 white cells per cubic millimeter, and 100 mg. of dextrose and 43 mg. of nonprotein nitrogen per hundred cubic centimeters. The Wassermann reactions of the blood and the spinal fluid were negative. The blood pressure was 126 systolic and 104 diastolic, and the temperature was normal. On the day preceding death it rose to 103.8 F., the pulse rate was 150 and the respiratory rate was 40. Bronchopneumonia set in (Feb. 3, 1939) and was followed by death on February 4, the day the patient was to have been operated on for a subdural hematoma.

*Necropsy* (Dr. W. O. Brown).—The brain weighed, 1,300 Gm. The dura was dull and lusterless, of purplish gray color. It was distended by a large quantity of unclotted, dark purple blood, which measured 80 cc. It was distributed bilaterally over the cerebral cortex, the greater amount being on the right side. The normal curvature of the cortex was flattened into a central ridge with flat, sloping sides, and the entire cortex was covered by a thin, dull brown pellicle. The base of the brain was free of blood. The arteries of the circle of

Willis were patent and appeared normal. The ventricles were normal and free of blood, and the "structures in their bases also appeared normal." The diagnosis was subdural hematoma with compression and flattening of the cortex. Hypostatic bronchopneumonia and central necrosis of the liver were also observed.

The brain was delivered to the laboratory without the dura. Dr. Milton Tinsley furnished additional information. In a note he stated that "postmortem examination showed a subdural hematoma which was not evident at the time the brain was cut (February 27), since it had been washed away by the fixing fluid. At autopsy the under surface of the dura over both hemispheres was covered by a thin, yellowish membrane. Under this membrane was a large collection of dark brown fluid, most of which was on the right side. Both hemispheres were markedly compressed by the fluid. When the dura was opened and the membrane underneath punctured, this dark fluid escaped freely."

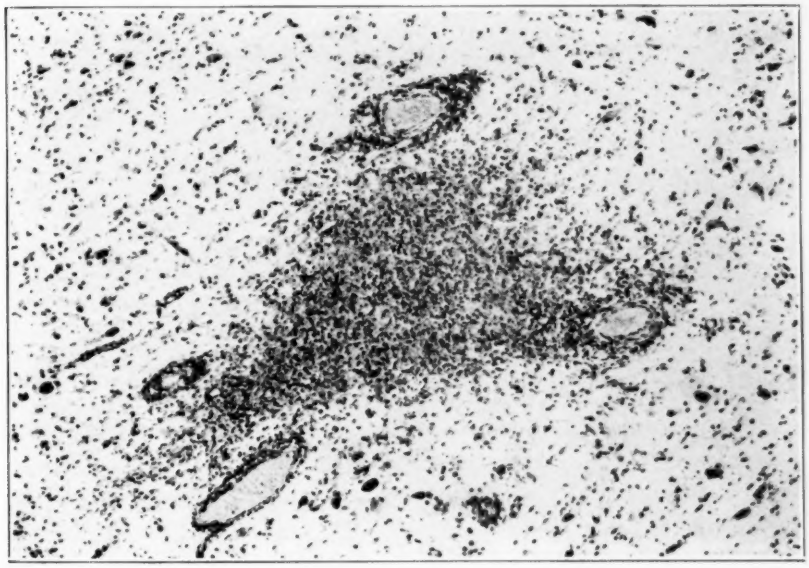

Fig. 9 (case 3).—The triangular focus of degenerative softening bordered by several infiltrated and patent blood vessels. Toluidine blue stain.

One gains the impression that the fluid was not encysted, and it should be assumed that the blood clot became liquefied and the neomembrane thickened.

Transverse sections revealed normal-sized ventricles, a hemorrhagic spot in the right internal capsule near the optic thalamus and numerous petechiae in the pons and the corpus striatum. The occipital lobe and cerebellum exhibited no changes.

*Microscopic Examination.*—Only the brain was available for study. In the medulla, in the region of the olives, on the right side was a focus of softening (fig. 9), triangular and bordered by several infiltrated but patent blood vessels. The focus, as in the preceding 2 cases, consisted of microglia gitter cells. Microgliocytes were present also in the remote healthy areas, while the perivascular infiltrations consisted of lymphocytes and gitter cells. Infiltrated blood vessels were present also in the pons, the subcortex of the frontal lobe and the right

optic thalamus, where they were mixed with numerous particles of calcium salts. The other parts of the cortex, such as the occipital lobe, exhibited numerous microgliocytes, mostly in the form of rod cells. The ganglion cells were occasionally swollen and exhibited phenomena of neuronophagia.

The meninges were infiltrated with polyblasts, fibroblasts, mesothelial cells and histiocytes filled with blood pigment. The subpial space over the frontal lobe contained histiocytes packed with pigment, colorless red cells and numerous chromatophores.

The pathologic changes may be summed up as a focus of degenerative softening of the medulla combined with extensive inflammatory phenomena.

## COMMENT

In the 3 cases here recorded the pathologic pictures were identical: foci of nonvascular, degenerative softening in the form of recent demyelination combined with pronounced inflammatory changes. Yet the clinical symptoms varied in each case. In case 3 the usual picture was obscured by a subdural hemorrhage which was not encysted and most likely had no bearing on the patient's condition. As Munro and Merritt [3] demonstrated so well, such subdural hematomas may remain unabsorbed and may not produce local signs of cerebral damage. For this reason, even if the operation for the removal of the hematoma had been carried out, it would not have prevented the fatal outcome, because of the focus of softening in the medulla oblongata. The softening was acute and probably was due to infected teeth.

Of the greater interest and easier of interpretation are the first 2 cases. In case 1, in which there was a Brown-Séquard syndrome, a diagnosis of tumor was strongly considered even at the operation, while in case 2 an inflammatory process—encephalomyelitis or, because of the presence of demyelination, multiple sclerosis—was suggested. The pathologic features in these 2 cases and in case 3 were intense perivascular infiltrations, foci of softening and normal blood vessels. Both the infiltrations and the demyelinated foci of softening were unique. The former consisted of lymphocytes, occasionally mixed with plasma cells and fat granule bodies (gitter cells); the foci of softening consisted of immense masses of microgliocytes, most of which were transformed into gitter cells, intermingled with numerous blood vessels. Nerve fibers were not in evidence; naked axons were scarce, but cytoplasmic astrocytes were occasionally abundant, while fibrillary astrocytes with formation of glial patches or scars of connective tissue, such as are seen in vascular softening (from thrombosis or embolism), were not present. In short, the islands of demyelination were neither of multiple sclerotic nor of vascular origin, but morphologically were typical of what has been termed multiple degenerative softening. The essential features of the

3. Munro, D., and Merritt, H. H.: Surgical Pathology of Subdural Hematoma Based on a Study of One Hundred and Five Cases, Arch. Neurol. & Psychiat. **35**:64 (Jan.) 1936.

latter—degeneration of the myelin and axons, with formation of fat granule bodies (gitter cells); perivascular infiltrations with hematogenous elements or gitter cells or both, in the presence of normal blood vessels and normal gray matter and in the absence of connective tissue proliferation—have been produced experimentally. Recently they have been excellently described by Rivers and Schwentker [4] and especially, by Ferraro and Jervis [5] in monkeys, into which they injected extracts of normal rabbit brain. Ferraro and Jervis conceded that the changes "fit well into the group of so-called multiple degenerative softening." The same may be claimed for the lesions in the brain of patients described by Grinker and Bassoe,[2] who expressed the belief that the condition was disseminated encephalomyelitis; it should, however, be included with multiple degenerative softening.

The perivascular infiltrations, which may sometimes be intense, are the result of demyelination and transformation of the destroyed nerve tissue into fat granule bodies (gitter cells). These ultimately reach the adventitial spaces of the blood vessels and capillaries, where they cause a lymphocytic reaction, termed by Spielmeyer symptomatic inflammation. As Ferraro and Jervis demonstrated,[5] the infiltrations may consist of gitter cells only or of lymphocytes and plasma cells only or of both hematogenous elements and fat granule bodies. This is true also of the cases in man. Whatever the type of the reactive cells, the primary cause is a toxic-infectious factor. In cases 1 and 2 an infection preceded the onset of the nervous manifestations, which in case 3 were preceded by extraction of infected teeth. It must be postulated that an unknown toxic factor directly attacked the nerve fibers, without the intermediation of the blood vessels, the process being analogous to demyelination produced experimentally by the action of antirabies vaccine,[2] extracts of brain,[6] tetanus toxin,[7] potassium cyanide,[8] postvaccinal virus,[9] and toxins from carious teeth and other factors.[10] An interesting feature was noted

4. Rivers, T., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689 (May) 1935.

5. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

6. Rivers and Schwentker.[4] Ferraro and Jervis.[5]

7. Putnam, T. J.; McKenna, J. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanus Toxin, J. f. Psychol. u. Neurol. **44**:460, 1932. Putnam, T. J.; Morrison, L. R., and McKenna, J. B.: Experimental Demyelination, Tr. Am. Neurol. A. **57**:451, 1931.

8. Ferraro, A.: Experimental Toxic Encephalomyelopathy, Psychiatric Quart. **7**:267 (April) 1933.

9. Hassin, G. B., and Geiger, J. C.: Postvaccinal (Cowpox) Encephalitis: A Clinicopathologic Report of a Case, Arch. Neurol. & Psychiat. **23**:481 (March) 1930.

10. Diamond, I. B.: Changes in the Brain in Pyemia and in Septicemia, Arch. Neurol. & Psychiat. **20**:524 (Sept.) 1928.

in all 3 cases. Localized as the demyelination was, signs of a general or systemic reaction in the form of universal microglial proliferation were always present. In case 1 the phenomenon was in evidence as far as the sacral region and the cerebellum, but caused no clinical signs or symptoms. Clinical manifestations were produced only by the primary foci, and as these may be located anywhere in the nervous system, the clinical picture caused by multiple degenerative softening varies greatly from case to case. Yet there are exceptions. Neuroptic myelitis, for instance, has a well defined localization and, accordingly, a well defined clinical and pathologic picture—a combined degeneration of the spinal cord and the visual system of fibers; encephalitis pontis and cerebelli of Redlich [11] always has some clinical signs of involvement of the pons or of both the pons and the cerebellum; Schilder's disease, so-called Baló's disease and Marchiafava's disease are probably also forms of multiple degenerative softening with a fairly constant localization; postvaccinal and postmeasles encephalitis—typical instances of demyelination in the nature of multiple degenerative softening—possess equally typical pathologic features, though differing somewhat from those of other types of degenerative softening, a subject to be discussed in a separate contribution. Here it should be emphasized that the difference in the pathologic aspects, and probably in the localization, is due to that of the virus or the noxious agent, which must vary in each individual form or case of multiple degenerative softening. Elsewhere [1c] it has been stated that, like multiple sclerosis, multiple degenerative softening is a specific morbid entity caused by toxic factors which attack the nerve fibers directly, without the intermediation of vascular factors (endarteritis, embolism, thrombosis, arteriosclerosis and other changes); that multiple degenerative softening forms a separate group of subacute parenchymatous neural disorders, and that

> though [the latter] possess a common feature, the areas of demyelination, they are nevertheless distinct morbid entities—as are poliomyelitis, epidemic encephalitis, encephalitis following typhus and dementia paralytica, which are recognized specific morbid entities, though they also possess a common feature, perivascular infiltration. As each member of the second group is thought to be due to a specific infiltration, so each member of the first group is probably due to a specific intoxication. It is true that the exact nature and name of the toxins in the majority of the forms [of multiple degenerative softening] are not known, [but] neither is the exact nature of some infectious diseases (such as smallpox, rabies and poliomyelitis); yet they are universally classified as such.

The factors brought forth in the present contribution seem to bear out the correctness of the aforementioned views.

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11. Redlich, E.: Ueber Encephalitis pontis und cerebelli, Ztschr. f. d. ges. Neurol. u. Psychiat. **37**:1, 1917.

## CONCLUSIONS

Three cases of disseminated degenerative softening have been studied clinically and pathologically.

The clinical features were indefinite and varied in each case, but the pathologic features were definite and similar in the 3 cases.

The essential pathologic features were a combination of demyelination and inflammatory changes.

The demyelination was in the nature of degenerative softening, caused by the direct action of a toxin on the nerve tissue, and was not of vascular origin.

The pathologic features of multiple degenerative softening can be produced experimentally by injecting into animals foreign substances, such as extracts of brain tissue.

# DIETETIC AND RELATED STUDIES ON MULTIPLE SCLEROSIS

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It seems fairly clear that certain known circumstances have an influence on the course of multiple sclerosis. Those usually mentioned are infection, pregnancy, chilling, toxemia, emotional disturbance and trauma, the importance of all but trauma being well attested. Also, in recent times, the possibility that there may be a nutritional element has been rather widely discussed, although Dattner [1] alone has formally suggested it. Others, especially Goodale and Slater, Stern and Moore, have implied such a factor by treating patients with liver or vitamins. The experiments on animals of Mellany and of Zimmerman have suggested a similar possibility. It must be admitted, however, that the actual evidence favoring this point of view is still meager. Actual studies of the diets of patients with multiple sclerosis have not been made.

Our attention was focused on this phase of the problem by the statement of a patient with multiple sclerosis that he rarely ate butter. The subsequent observation that this was true of several other patients with the same disease led us to undertake a detailed study of the nutritional habits of patients with multiple sclerosis. The purpose of

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1. Dattner, B.: Zur Pathogenese der multiplen Sklerose, Wien. klin. Wchnschr. **50**:87-92, 1937.

this paper is to present the results of that study, as well as some additional facts which appear relevant.

## DIETARY HABITS OF PATIENTS

*Method of Obtaining Data.*—Information was sought in two ways. First, the patients' histories were studied in order to obtain a qualitative picture of their dietary habits and of the relation between this and other features of the history to the course of the disease. Second, an attempt was made to put into quantitative form all of the data bearing on the dietary habits. The latter method proved to be not wholly satisfactory, for reasons to be presented later. The qualitative study gave more reliable results.

Thirty-four patients were subjected to an extensive inquiry concerning their dietary habits in various periods of life, such as those of high school, college, employment, time away from home and marriage. Many parts of the story, particularly that concerning the foods which were habitually not eaten, could be told with what was probably a reasonable degree of accuracy. The patients were usually young, so that the account generally concerned a relatively recent period.

The veracity of the essential points in the dietary histories was tested and corroborated in four ways: (1) by the patients' general statements concerning their attitudes toward food; (2) by the statements of parents, siblings, husband or wife; (3) in 14 cases, by the recording of actual food intake prior to treatment (referred to as "spontaneous" diet records), and (4) in 17 cases, by the recording of actual intake of prescribed diets designed to compensate for the defects (referred to as "regimen" diet records).[2]

*Results of Qualitative Dietary Survey (Table).*—The estimates of the food intake were compared in each instance with the patient's supposed caloric requirements, with due regard to his level of activity. In this connection it may be noted that the material was derived chiefly from patients who were not incapacitated. Most of the patients in the series were regularly employed in stores and offices. Many of the others were well enough to continue their full quota of housework. Others worked, but only part time. Many were in clearcut remissions; some of these were free from symptoms, while others suffered from residua of previous attacks. Only 13 were confined to a chair or were bedridden, and among these the food intake was still far less than the criteria for such persons call for. The histories extended back usually to a time prior to the first onset of the disease and always to periods of complete remission, prior to subsequent attacks. For all of these reasons, it is

2. The records were kept on special sheets supplied in large quantities by Eli Lilly & Co., Indianapolis.

thought that the data truly indicate the food habits of the patients and are not indicative merely of the changes in habits produced by chronic illness.

*Summary of Qualitative Dietary Survey* *

| Case No. | Diet † | Fats: Patient Had Aversion | Fats: Disagreed with Patient | Weight Status ‡: Underweight | Weight Status ‡: Ideal Weight | Weight Status ‡: Overweight | Weight Status ‡: Steady Loss | Weight Status ‡: Loss with Attack | Weight Status ‡: Gain Under Regimen | Food Change with Attack | Presence of Other Factors Before Attack § | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | + | .. | + | .. | .. | + | .. | + | + | + | Aversion to vegetables |
| 2 | 1 | + | .. | .. | + | .. | .. | .. | + | .. | + | Aversion to vegetables |
| 3 | 1 | + | .. | + | .. | .. | .. | + | ? | + | + | Aversion to vegetables; fills up quickly; feeding problem as child |
| 4 | 1 | + | .. | + | .. | .. | .. | .. | .. | .. | + | Fried foods disagree |
| 5 | 1 | .. | + | ⊕ | .. | .. | .. | .. | + | .. | .. | Poor appetite, finicky eater, aversion to vegetables; fills up quickly; feeding problem as child |
| 6 | 1 | .. | .. | .. | .. | + | .. | + | + | .. | .. | Feeding problem as child |
| 7 | 1 | — | .. | + | .. | .. | .. | + | + | + | + | Many food aversions; bad teeth; hurried eating |
| 8 | 1 | + | .. | .. | + | .. | .. | + | .. | +? | .. | |
| 9 | 1 | + | + | .. | .. | .. | .. | .. | .. | + | + | Poor appetite; abdominal pain; finicky; feeding problem as child |
| 10 | 1 | + | + | .. | .. | .. | .. | .. | .. | .. | .. | |
| 11 | 1 | ? | + | .. | .. | .. | + | + | + | + | .. | Feeding problem as child; gallbladder disease |
| 12 | 1 | + | + | ⊕ | ⊕ | .. | + | .. | .. | .. | + | Faddish refusal to eat |
| 13 | 1 | + | + | ⊕ | .. | .. | .. | + | .. | + | .. | |
| 14 | 1 | + | + | + | .. | ⊕ | .. | + | .. | + | .. | Poor teeth; reducing addict; feeding problem as child |
| 15 | 1 | — | .. | .. | .. | .. | .. | .. | .. | .. | .. | Reducing addict |
| 16 | 1 | + | + | .. | .. | + | .. | .. | .. | .. | .. | |
| 17 | 1 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | Aversion to vegetables |
| 18 | 2 | + | .. | .. | + | .. | .. | + | + | + | + | Fussy eater; ulcer |
| 19 | 2 | + | .. | ⊕ | .. | .. | .. | .. | .. | +? | + | |
| 20 | 2 | + | + | + | .. | .. | + | .. | + | — | + | Finicky eater |
| 21 | 2 | — | — | .. | ⊕ | .. | .. | + | .. | + | .. | |
| 22 | 2 | + | .. | .. | + | .. | .. | +? | .. | + | + | Bad teeth; reducing addict |
| 23 | 3 | + | .. | .. | + | .. | .. | .. | + | .. | .. | |
| 24 | 3 | .. | .. | + | .. | .. | .. | + | .. | .. | + | |
| 25 | 3 | .. | .. | .. | .. | + | ? | .. | .. | + | + | |
| 26 | 3 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | Aversion to vegetables |
| 27 | 3 | — | .. | .. | .. | .. | .. | .. | .. | .. | + | |
| 28 | 3 | . | .. | .. | .. | + | .. | .. | .. | .. | — | Aversion to vegetables |
| 29 | 3 | ? | .. | .. | .. | .. | .. | .. | .. | .. | .. | |
| 30 | 3 | .. | .. | .. | .. | ⊕ | .. | .. | .. | .. | +? | |
| 31 | 4 | — | — | .. | .. | + | .. | .. | .. | .. | + | |
| 32 | 4 | — | — | .. | .. | + | — | .. | .. | .. | +? | |
| 33 | 4 | — | .. | ⊕ | .. | .. | .. | .. | .. | .. | .. | |
| 34 | 4 | — | — | .. | .. | + | — | — | .. | + | — | |

* Blank spaces (..) in the table mean that dependable information was lacking, except in the column headed "Gain under Regimen," in which blanks almost always mean that the patient did not follow the regimen.

† This column shows to which group patients belonged from the standpoint of dietary adequacy.

‡ The weight status refers to long periods, antedating at least the attack in which the patient was seen, except when the plus sign is encircled, in which instance the weight record was for a period starting under our supervision.

§ "Other Factors" refers to infection, prolonged overwork, emotional strain, etc., described in the text.

The cases are divided into four groups: (1) those in which there were obvious dietary peculiarities which really amounted to deficiencies or inadequacies (17 cases); (2) those in which the histories bear evidence highly suggestive of such limitations (5 cases); (3) those in

which the evidence is not convincing, but some indications of disturbance, usually of similar nature to the disturbances in groups 1 and 2, were presented (8 cases), and (4) those in which no suggestion of abnormality could be found (4 cases).

Groups 1 and 2: In 17 cases the stories told by the patients obviously suggested, and in 5 other cases strongly pointed to, dietary peculiarities. In every case the stories were corroborated by parents, siblings, husband or wife. The corroborated peculiarities had often dated back to the earliest remembered days of life, in all but 3 cases to times prior to the onset of the disease and in the others at least to a period long prior to the attack in which the patient was seen.

The evidence was, first, that the patients in general were poor eaters. This was strikingly true of all patients in group 1. Eighteen patients were especially poor users of visible, and particularly of dairy, fats. Sixteen had an outspoken aversion to visible, and specially to dairy, fats, 1 patient even declaring, "If my future depends on eating butter, I'll resign myself to my fate." It should be noted that the known aversions to fats were almost all in groups 1 and 2, with 1 patient in group 3 and none in group 4 (table).

Additional reasons for inadequate eating were: a chronic desire to lose weight or to stay thin (cases 14, 15 and 22); a tendency to "fill up quickly" (cases 3 and 5); pyloric ulcer (case 18); abdominal pain, relieved after many years by an operation for fistula in ano (case 9); gallbladder disease (case 11); a fad (case 12), and in part, lack of time for eating (case 7).

Butter, milk and eggs were the articles most frequently omitted. Many patients who otherwise consumed little or no dairy fat did take cream, especially, and sometimes ice cream, occasionally in ordinary or greater quantities.

Five of the patients in group 1 also had an aversion to vegetables, as did 2 patients in group 3.

Six patients, all in group 1, are known to have presented feeding problems in infancy or childhood.

Group 3: Of the remaining 12 patients, 8 belong in group 3. Of these, the histories of 5 suggested relatively deficient intakes of dairy fats (1 patient, for example, had long believed herself allergic to many types of fat, including the dairy variety, and had been experimenting accordingly for a long period). Of the remaining 3 (cases 25, 28 and 30), 1 was on relief and could not have had a highly adequate diet, although he stated that he did; he was, it is true, chronically overweight; this was attributed to a very high carbohydrate intake, chiefly in the form of spaghetti. This patient was the only one in the entire series whose statements might have been unreliable. In case 25 there was a history which

was too varied for interpretation. One attack, however, was linked with the dietary reduction to be discussed later. In case 28 (and also in case 26) the patient had an aversion to vegetables and ate them in small quantities.

Group 4: Only 4 patients (cases 31, 32, 33 and 34) presented substantiated histories and supporting evidence absolutely free of the suspicion of some degree of dietary insufficiency.

Relation to Weight: The dietary histories were, in general, corroborated by the weight records. Of the 17 patients in group 1, adequate, dependable weight records were available for 13. Of these, 8 are, and 5 have long been, between 8 and 41 pounds (3.6 and 8.6 Kg.) underweight. Two patients (cases 2 and 8) have remained near their ideal weight, except that during one attack the patient in case 8 was 11 pounds (5 Kg.) below the ideal level. The patient in case 16, who has an endocrine disturbance, is obese, and the patient in case 6 has remained slightly above her ideal weight. Three patients for whom extensive weight records are available have had a steady loss of weight over a long period. Of the 5 patients in group 2, 3 have remained near the ideal level, 1 has long been underweight and the single measurement of the remaining patient showed her to be 9 pounds (4.1 Kg.) underweight. Of corresponding interest is the fact that 2 of the 8 patients in group 3 and 3 of the 4 patients in group 4 have long been 5 to 23 pounds (2.3 to 10.4 Kg.) overweight. Of the rest of the patients in group 3, 1 was overweight in her single measurement, 1 has remained near the ideal level (case 23) and only 1 was underweight. In general, then, the weight corresponds with the dietary history. The greatest degree of underweight was among those with the most striking histories of deficiency, and most of the cases of overweight were in the group with the best dietary histories (table).

Further corroboration is afforded by the fact that all observed patients gained in weight after a corrective dietary regimen was instituted. Nine patients from this series who have been placed on such a regimen are frequently seen and weighed. All of them have gained weight to a striking degree, starting with the institution of the regimen. This is true even though only 2 of them are adhering well to the regimen—a fact which again reflects the attitudes of many of the patients to food. Three have flatly refused to increase their food intake at all, even though they know fully the threat they live under. Of those who have accepted the regimen, many evade it frequently and need continued pressure in order to adhere to it at all.

*Results of Quantitative Dietary Survey.*—The data were obtained by the best methods available to us, but it is thought, nonetheless, that the information is not, and could not be, sufficiently accurate to warrant

arithmetical treatment. For purposes of such a study, it would be necessary to weigh all the food of hospitalized patients. Although the material was translated into figures, since it could not be visualized in any other way, we have employed these figures only for the sake of the trends they reveal and for general corroboration or noncorroboration of the histories. The figures do support in full the trends discovered in these histories.

In order to evaluate the figures, so that they could be used for the purposes just mentioned, certain criteria were employed. The criteria with which our patients' intake of specific food items and of total fat, carbohydrate and protein were compared were taken from the work of several investigators, particularly that of Stiebeling and Phipard.[3] These authors, who have made extensive investigations of American dietary habits, included in their studies analyses of one week's food consumption of 373 families of white employed wage earners and clerical workers in North Atlantic American cities. Their data were obtained by calculating the amounts purchased by families with various expenditures for food.

The value of the figures derived from such studies as controls for an investigation such as ours is attested by the work of various other authors.[4]

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3. Stiebeling, H. K., and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities, Circular 507, United States Department of Agriculture, 1939.

4. (*a*) Wheeler, R., and Shalla, E.: A Nutritive Analysis of Hospital Food Bills, J. Am. Dietet. A. **2**:10-27, 1926. (*b*) McLester, J. S.: Nutrition and Diet in Health and Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1939. (*c*) Hoskins, R. G.: American Military Hospital Dietaries, Am. J. Physiol. **49**:578-587, 1919. (*d*) Smith, F. H., and Biltz, B. J.: A Comparison of the as Purchased and Prepared Food Methods for Determining the Food Intake of Hospital Patients, J. Am. Dietet. A. **8**:107-118, 1932. (*e*) Sherman, H. C., and Gillett, L. H.: The Adequacy and Economy of Some City Dietaries, Publication no. 121, New York Association for Improving the Condition of the Poor, 1917. (*f*) Pearl, R.: The Nation's Food, Philadelphia, W. B. Saunders Company, 1920. (*g*) Cathcart, E. P., and Murray, A. M. T.: A Dietary Survey in Terms of the Actual Foodstuffs Consumed, Medical Research Council, Special Report Series, no. 218, London, His Majesty's Stationery Office, 1936. (*h*) Cathcart, E. P., and Murray, A. M. T., assisted by Shanks, M.: Studies in Nutrition: An Inquiry into the Diet of Families in Cardiff and Reading, Medical Research Council, Special Report Series, no. 165, ibid., 1932; (*i*) A Study in Nutrition: An Inquiry into the Diet of One Hundred and Fifty-Four Families of St. Andrews, Medical Research Council, Special Report Series, no. 151, ibid., 1931. (*j*) Rose, M. S.: Feeding the Family, ed. 3, New York, The Macmillan Company, 1937. (*k*) Rose, M. S.: A Laboratory Handbook for Dietetics, ed. 4, ibid., 1937. (*l*) Waller, D. S.: Nutritive Value of Foods, Ann Arbor, Mich., George Wahr, Publisher, 1936. (*m*) Sherman, H. C.: Chemistry of Food and Nutrition, ed. 5, New York, The Macmillan Company, 1937. (*n*) Hodges, M. A., and Peterson, W. H.: Manganese, Copper, and Iron Content of Serving Portions of Common Foods, J. Am. Dietet. A. **7**:6-16, 1931. (*o*) Booher,

*(Footnote continued on next page)*

RELATION BETWEEN CHANGES IN FOOD INTAKE, WEIGHT AND COURSE OF THE DISEASE

*Food Intake and Clinical Course.*—Attacks occurred in 12 cases after changes in food intake. The only changes considered in the study were drastic, well attested ones, confirmed by circumstances of one kind or another. Some occurred while the patients were under our own observation, prior to our interest in nutrition. In such instances they had been under our care for many years, and although they were not necessarily observed during the weeks in which the change in food consumption took place, they were seen as soon as the attack occurred, when the dietary changes were so recent that there could be no doubt of the authenticity of the story.

In 2 cases the attack came during the drastic reduction in food intake (cases 7 and 11), but more commonly it occurred shortly after such a reduction had terminated, during the period when the patient was gradually increasing his food consumption. Since the actual amounts of food involved in these episodes had to be obtained from histories instead of weighed samples, accurate figures are lacking. It is possible, however, that the increases in food were unbalanced and that there was a relatively greater increase in calories than in vitamins, with an ensuing vitamin deficiency. The same may perhaps be said for those instances in which there was a drop in food intake without a subsequent increase. Two of the attacks in 1 case (case 14) are known to have occurred during periods of excessive increase in consumption of vitamin-poor carbohydrates. The qualitative facts are definitely known in these instances, although the exact quantitative data are not. Details are given in the case histories, which are outlined below. That such imbalances, resulting in too low vitamin $B_1$–calory ratios, may cause at least vitamin $B_1$ deficiency is widely accepted. A full discussion of this subject appears in the writings of Cowgill,[4s] Williams and Spies,[4t] Eddy and Dalldorf,[4u] Jolliffe[4v] and others.

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L. E., and Hartzler, E. R.: The Vitamin $B_1$ Content of Foods in Terms of Crystalline Thiamin, Technical Bulletin 707, United States Department of Agriculture, 1939. (*p*) Daniel, E. P., and Munsell, H. E.: Vitamin Content of Foods, Miscellaneous Publication 275, United States Department of Agriculture, 1937. (*q*) Bridges, M. A.: Dietetics for the Clinician, ed. 3, Philadelphia, Lea & Febiger, 1937; (*r*) Food and Beverage Analyses, ibid., 1935. (*s*) Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934. (*t*) Williams, R. R., and Spies, T. D.: Vitamin $B_1$ (Thiamin) and Its Use in Medicine, New York, The Macmillan Company, 1938. (*u*) Eddy, W. H., and Dalldorf, G.: The Avitaminoses, Baltimore, Williams & Wilkins Company, 1937. (*v*) Jolliffe, Norman: The Influence of Alcohol on the Adequacy of the B Vitamins in the American Diet, Quart. J. Stud. on Alcohol **1**:74-84 (June) 1940.

*Weight and Clinical Course.*—Records of the past weights of the patients were employed when it was possible to obtain accurate information. As already stated, weight histories and actual current weight measurements in general coincide with the records of caloric intake. Sufficient information was available for comparison of the weight history with the severity of the clinical course in 21 cases. There appears to be a correlation between weight and intensity and speed of involvement. The underweight patients have, as a whole, done much less well than the overweight ones, and even than those who have remained near their theoretically ideal weights. This applies regardless of the patient's grouping. In 1, or possibly 2, of the underweight patients, the underweight may have been due to chronic invalidism, but in the remainder it anteceded the onset of the disease. Some of the overweight patients have been sick for many years, but are still overweight, despite the fact that some of them are now chair ridden.

Multiple sclerosis is generally thought to be unusual in obese persons. Our series, although it bears out this belief in general, nonetheless includes 5 patients who are definitely obese and who have had the disease for many years. These 5 persons (cases 16, 25, 30, 31 and 32) have had slow and favorable courses. In case 32 the patient is now chair ridden, but his disease began in 1916, he remained at business until 1933 and he became chair ridden only in 1935.

Thirteen attacks in 10 patients are known to have been associated with an acute loss of weight. The loss of weight is known to have anteceded the attack in 9 instances. Improvement has been associated with gain in weight in 8 patients, but in only 1 (case 34, group 4) has improvement been linked with loss in weight. Regression with known gain in weight has been observed in 2 patients (case 14, group 1, and case 34, group 4); in case 14 the gain in weight appears to have been due to the sharp increase in carbohydrate intake. In case 34 the gain was coincident with gradual departure from a low fat diet.

## TREATMENT

The therapeutic regimen consisted of: (1) a nutritious and well balanced diet, in so far as it was possible to persuade patients to adhere to it; (2) maintenance doses of thiamine hydrochloride, vitamin B complex, riboflavin, haliver oil and wheat germ oil (vitamin $B_6$ is now available for special trial[5]), and (3) large doses of single preparations given to various groups of patients, in an effort to discover which may be the most valuable. It has not as yet been possible to draw conclusions.

5. The following firms are now supplying vitamin products: E. R. Squibb & Sons, riboflavin; Hoffmann-LaRoche, Inc., alpha tocopherol; Merck & Co., Inc., vitamin $B_6$ and alpha tocopherol, and the International Vitamin Corp., vitamin B complex and wheat germ oil.

### INTERCURRENT EVENTS

Certain characteristic types of events were found to have anteceded some attacks of the disease. In general, in cases in which an intelligent patient could give a credible history, it was found that attacks were often anteceded by a prolonged period of overwork or emotional strain or both, with exhaustion; an infection, such as an abscess, influenza, a cold or other disease of the upper respiratory tract, or chilling. Pregnancy is, of course, also a well known precursor of attacks. These events are described more fully in the case histories that follow. Such events or changes in food intake or both are known to have occurred in connection with at least one attack in each of 20 cases.

Müller,[6] von Hoesslin and others have described similar observations. Siemerling,[7] reported that during the World War severe exertion, such as hard marching, sometimes produced paralysis of the lower extremities and coincident impairment of vision in soldiers. The occasional ill effects of lumbar puncture in cases of multiple sclerosis were pointed out by Dreyfus and Mayer [8] and were mentioned by Siemerling.[7] In the present series, such an event appears to have occurred three times (case 12, in which a regression is reported to have been associated with several days of vomiting after a lumbar puncture; case 13, in which a slight regression was associated with loss of weight after a puncture, and case 20, in which a severe relapse followed a second intrathecal injection of vitamin $B_1$).

Müller, as well as many others, has mentioned trauma as a precipitating event. Strümpell [9] reported a series of cases in which the disease was apparently precipitated by severe falls on the back. Our evidence concerning trauma is not convincing to us, although the data offer enough indications of its importance to prevent its exclusion. It has seemed remarkable that several patients experienced surgical operations, including some with spinal anesthesia, without ill effect. In 2, however (cases 1 and 12), regression followed operation. With regard to pregnancy, 1 patient (case 21) bore a child during a remission, with no sign of recurrence. In another, case 23, the disease began a full year after the end of a successful pregnancy.

All of the factors which have been presented are summed up, and perhaps visualized best, in the case histories which follow.

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6. Müller, E.: Multiple Sklerose, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1925, vol. 5, pt. 1, p. 681.

7. Siemerling, E.: Multiple Sklerose, Klin. Wchnschr. **15**:609-612, 1924.

8. Dreyfus, G. L., and Mayer, K.: Vier Jahre Malariabehandlung der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **111**:68-98, 1929.

9. Seyfarth, C., and Strümpell-Seyfarth: Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten, Leipzig, F. C. W. Vogel, 1930, vol. 2, pp. 546-556.

REPORT OF CASES

CASE 1.—A married man aged 46 had for a long time been on a diet which was generally poor, especially in fats. The onset of his illness, in 1910, was associated with a boil and with the ingestion of many cathartics. In 1914 a questionable attack was precipitated by marked loss of sleep and dietary reduction. The patient had deliberately taken excessive amounts of cathartics and caffeine to make himself unfit for military duty. In 1923 further regression followed irregular eating after the death of his wife and the excessive taking of cathartics. In 1929, after business reverses connected with the Wall Street crash, overwork, worry and irregular eating, there was still further regression. An operation in 1935 and a cold in 1937 anteceded other attacks. The disease was still not extremely advanced in 1939, when improvement began for the first time, after the patient was placed on a corrected dietary regimen. According to the scattered measurements available from his history, he had been chronically underweight.

CASE 3.—A man, whose diet had habitually been inadequate, had his second attack of multiple sclerosis after influenza. This attack was of special interest, being similar perhaps to the second one in case 34 and possibly to the attacks in cases 14 and 25, just described. His appetite and weight had decreased for about one month, at the end of which there was some improvement in both. After a week in which he ate better a severe attack of multiple sclerosis occurred. An additional feature in the case was that in the ten days prior to the attack he had had eight drinks of rye whisky, a beverage he had used frequently in the past but which he had avoided since, nine months prior to the attack, he had been found by cutaneous tests to be sensitive to rye. This is the only attack in the whole series in which allergy may justifiably be suspected of playing a role. The patient had presented a feeding problem in childhood.

The fourth attack followed another extreme reduction in food intake and in weight, with no known period of improvement in eating before the attack came on. Food always caused him to "fill up quickly."

CASE 4.—A woman aged 30, who had had a chronically insufficient diet, is the patient who spoke of accepting her fate in preference to eating butter. She has had twelve attacks and regressions. The first attack followed a year of fatigue with sleeplessness. The second came during an intense emotional disturbance, immediately after she had driven a car to Florida; during this trip she traveled 600 miles (965.5 kilometers) in one day, with little to eat throughout the journey. The fourth came during her wedding trip. Information is lacking about the remaining episodes, except the most recent, a regression associated with the administration of the prescribed dietary regimen, which the patient followed only partially.

CASE 7.—A white woman aged 27 had had at best a borderline diet for many years. Fats, particularly dairy fats, were especially poorly represented. In 1935 an unhappy marriage became a source of serious trouble, terminating in divorce, which left the patient in debt. In October 1937 she went to work in a store and, in order to earn extra money for the payment of the debts, worked at night at least four times a week. Breakfast was taken on the way out of the house, and a hurried sandwich lunch was eaten, all in an effort to be at the store as much as possible. Supper on the four working nights consisted of leftovers. The patient became exhausted and lost weight. Her first attack occurred in December 1937. Rest, improvement in nutrition, and gain in weight were associated with a return to normal.

In the summer of 1938 she had a hectic love affair, in which she was trailed by detectives and which terminated with the display of a gun and the threat of suicide by her lover. Again she found herself in debt. The cycle of the previous year was repeated, and a second attack of the disease occurred three months later, again with return to normal on a regimen of rest and good nutrition, with gain in weight. The patient had become 15 pounds (7.5 Kg.) underweight at the onset of each attack.

Case 8.—One of the four attacks of this patient was anteceded by the administration of a metal-free diet with ammonium chloride for a few days.

Case 9.—A man aged 42, married, had his first attack in 1918, while teaching at a college in Turkey. The food had become poor and scanty because of the war. At the time, he was teaching both music and mathematics and was conducting an orchestra. Also, army representatives were constantly seeking such persons as himself for army service, and he was constantly dodging them. The combination of circumstances was a considerable strain. The second attack occurred on arriving in the United States, after one month at sea, with inadequate diet. The third attack, insidious in onset, came during a long period of finicky eating due to chronic abdominal pain. There was continued slow regression, accentuated at and after his marriage, with a slow gain of 35 pounds (15.9 Kg.), possibly associated with an increase in vitamin-poor foods.

The patient had always had an aversion to fats and said that cream disagreed with him. His appetite had been poor since 1919. From 1924 to 1934 he was especially finicky in eating because of chronic abdominal pain. This was much improved by an operation for fistula in ano in 1931, but did not disappear until 1934. Hyperglycemia had been found in 1932, but not again. The patient had presented a feeding problem in childhood.

Case 11.—A woman aged 31, married, had similarly been on a low food intake, especially of dairy fats, for many years. Intake of potatoes, vegetables, bread and cereals had also been very low for years. All of these statements were supported by data from the history and from the "spontaneous" and, especially, the regimen diet records. This patient was one who rebelled against increasing her food consumption.

In November 1938 she had had attacks of epigastric pain, especially after eating fatty or fried foods. Gallstones were found. On December 1 she was placed on a fat-free diet, with relief of the abdominal symptoms. It is of interest that the carbohydrate intake rose while the patient was on this regimen. She lost 15 pounds (6.8 Kg.). Toward the end of December, while still on the fat-free diet, she suffered her first attack of multiple sclerosis. The diet was discontinued partially on Jan. 1, 1929, but she still omitted butter and fried foods. The course of the disease was fluctuant until April and unremitting in May and June. Improvement occurred in August, and by September she was almost well, after having gained 10 pounds (4.5 Kg.). Improvement was coincident also with typhoid vaccine therapy. The second attack followed an emotional upset, with no known change in the dietary regimen. There was excellent, but partial, recovery on the institution of an adequate food regimen with the administration of average to large doses of all the known vitamins except C, D and K. This program was interrupted by a gastric upset, during which the food intake was reduced by about one half for seven days, after which there was a relapse. Marked improvement occurred again after the dietary and vitamin regimen had been reinstituted.

This patient presented a feeding problem as an infant, "never being hungry." She has always had an aversion to fats, as had her father. She disliked walking

as a child. She has had periodic headaches, possibly migrainous. She is easily nauseated and vomits readily.

CASE 12.—A man aged 22, single, had had his first attack in August 1933. His dietary history was bizarre. He presented a known feeding problem, and for years, prior to the development of our interest in nutrition, his faddish unwillingness to eat and his equally faddish insistence on undergoing as much rigorous exercise as possible were the despair of his mother. His condition had been regressing slowly, but he was still able to take long walks, when, in late February 1936, he had a severe cold. A regression promptly set in, which continued unremittingly until, by the middle of 1939, he had become completely incapacitated. Throughout he continued to exercise and to take what was virtually a starvation diet. His weight dropped steadily, being 157 pounds (71.2 Kg.) at the end of September 1934, 126¼ pounds (57.3 Kg.) by Jan. 4, 1936, before the cold, and 98½ pounds (44.7 Kg.) on Sept. 8, 1939. One early regression had followed several days of vomiting, after a lumbar puncture. One regression had followed appendectomy.

CASE 13.—A married woman aged 39 had had a low food intake, especially with regard to visible fats, for many years. Beginning in 1929, she had been bloated and uncomfortable after eating rich, creamy or buttery foods, so that there was a continued and steady decrease in the intake of these items until the level of dairy fats reached a very low point (a statement supported by figures). For two weeks prior to her first attack, in January 1932, her "nose was stuffy" and she lost weight. Such information is available concerning only the first of this patient's nine attacks. One slight regression, associated with loss of weight, followed a lumbar puncture.

The patient had had an unsteady gait as a child. It is also stated that her 2 children were made ill by her milk long before the disease began.

CASE 14.—A woman aged 27, single, had her first attack in July 1927, at the age of 15. The onset was severe, with rapid and continued regression. Although no immediate preliminary circumstantial episode is known, her dietary history is of interest. About one and a half years prior to the attack she manifested a severe obsession to lose weight. She took many cathartics and ate little at meals. Between meals she stuffed herself with candy and pastry, in the belief that they would not fatten her and with the aim of having no appetite at meals. She lost a good deal of weight. The use of cathartics had been stopped many months prior to the first attack, but the dietary imbalance continued until six months after the illness began. She improved slightly in 1930 and markedly in 1931; no relevant data are available in connection with this remission, except that the patient stated there was no associated gain in weight. Then, for over a year, starting late in 1932, her diet was altered to consist almost entirely of cake and cornstarch pudding. On this regimen she gained weight, but had another severe attack of the disease, from which she has never recovered.

This patient presented a feeding problem in infancy and had had rickets. Ice cream had disagreed with her as a child. She had always had an aversion to fats, except that in childhood she liked butter. There had been much dental trouble since the illness began; according to her diary, she had fifty-two fillings between July 14, 1933 and Jan. 1, 1939. Operation for fistula in ano was performed during the course of the illness, with no adverse effect on the multiple sclerosis.

CASE 17.—A man of 56, who had received a chronically inadequate diet, had his first attack while working very hard as an intern and his third after influenza. Information is lacking concerning his other four attacks and three regressions.

CASE 18.—A married man aged 49 had always had an aversion to fats. He ate no butter as a child and had always had a low intake of dairy fat. Of interest is the fact that his father also had an aversion to fats. The patient had a pyloric ulcer in 1923 and fistula in ano in 1936. There was a history of asthma in childhood.

His first attack of multiple sclerosis, in the latter part of 1932, was associated with a carbuncle of the neck and loss of weight. A recurrence in 1935 was preceded by a period of anxiety and loss of appetite and sleep. The patient never recovered from this attack. In 1936 diplopia developed in association with a chalazion. In 1939, while on a vacation, he was told by a physician in another city that he had a dreadful and crippling disease and should immediately stop working. He was completely unnerved by this episode. He lost his appetite and frantically drove back to New York—a long and exhausting trip. A new attack developed immediately, after which he gradually improved, except for another slight, transient regression brought on by a cold. The patient had usually remained near his ideal weight.

CASE 19.—An unmarried woman aged 32 had an aversion to dairy fats, which was reflected in an extremely low intake. The general diet was also poor. The onset of her illness began in 1927, one month after her father died. The patient stated she was not much affected by his death. Between 1933 and 1939 there were many brief attacks associated with colds and sore throat, fright, loss of appetite and weight, the death of her mother, overwork, sleeplessness and depressions. The patient was chronically underweight.

CASE 20.—A man of 39 has had two attacks and two regressions. The diet has been fairly adequate. The first attack came during a period of intense worry. Two artificial fever treatments were associated with slight relapses. A severe second attack followed a second intrathecal injection of vitamin $B_1$, but there was rather prompt recovery, which was not impeded by a herniotomy performed with local anesthesia. Further improvement occurred when his physician ordered more food, and still more with the administration of the prescribed regimen. This patient is one of the few who accepted the regimen completely and readily.

CASE 21.—A woman aged 29 had had a fairly adequate habitual diet. She passed through a pregnancy between two attacks of multiple sclerosis without ill effect and was overweight prior to her second attack. For unknown reasons, her appetite became impaired and she lost weight. The attack came on after this condition had been present for one month. Appetite did not improve, and further loss in weight occurred, the total loss being 14 pounds (6.4 Kg.) in three months. The prescribed dietary regimen was adopted readily several months later, and complete recovery was associated with its administration.

CASE 22.—A woman aged 58, married, had her first episode of illness in 1904, within a year after marriage, possibly during pregnancy. A second episode occurred on a boat trip to the West Indies, in 1913. In 1929 there was slight, insidious progression, with no known antecedent event. Throughout her adult life the patient had been addicted to the idea of losing weight, undertaking repeated stringent reducing diets and using cathartics, especially salts, continually, but never with

much sustained loss in weight. Throughout she had remained close to her ideal weight. Her fourth episode, the first severe one, came directly after a long automobile drive, anteceded by five days of drastic reduction in food intake. The fifth and sixth attacks, both severe, occurring in December 1933 and February 1939, followed cystitis, with fever and infected urine. From every episode but the last recovery was excellent. Even after the last one, thirty-five years after the initial symptom, the patient resumed a degree of indoor walking, but her bladder function has remained poor. The fact that she was still leading a relatively active social life until 1933, and a fairly satisfactory one from that time until February 1939, shows how slowly the disease progressed. On Aug. 16, 1939 she had cerebral thrombosis, from which she recovered partially, and subsequently was able to stand with the support of one person.

The patient had an unsteady gait as a child and did not like walking or, later, dancing. She has almost always had an aversion to butter. Spinach is said to give her giant hives.

CASE 24.—A woman aged 31, who was chronically underweight, had had no detectable dietary insufficiency of note. Of four attacks, one was preceded by overwork with exhaustion and a loss of 5 pounds (2.3 Kg.) in two weeks. Recovery was associated with a gain of 6 pounds (2.7 Kg.) in weight. Another attack came the morning after a long automobile drive, during which she drove the car. There was no exhaustion, according to her statement, but the episode is mentioned because attacks in other patients have promptly followed long drives.

CASE 25.—A man aged 37, married, had his third attack of the disease on Jan. 16, 1939. Prior to this attack the disease had been in remission, and although he still suffered from residua, he was doing a full day's work as a clerk. His diet had been fairly adequate. Starting at Christmas 1938, he had overeaten greatly of candy and cake, taking freely the various holiday sweets that were in the house and reducing his intake of other foods. Coincidentally, he had insufficient bed covering and was chilled every night; laziness kept him from correcting this. Similar to the situation in case 14, the attack was anteceded by an increase in carbohydrate, at the expense of other foods. Information is lacking concerning the other two attacks.

The patient had had a severe injury to the head, with two hours of unconsciousness, and a tuberculous kidney many years prior to the onset of the illness. Spinach has always given him diarrhea.

CASE 31.—A single man aged 31, a physician, had an adequate diet. His illness consisted of many sudden, mild, transitory attacks. Disability has never been pronounced. At present his condition is virtually normal. A majority of the attacks were anteceded by overwork, fatigue, long drives, exposure to cold, sleeplessness and tension. For example, he had taken repeated long drives over icy roads, all within a few days, to care for a very sick patient in the country, and then had an attack. He was chronically obese.

CASE 32.—A man of 56, who was obese and had received a fairly adequate diet, had his first attack in 1916, after the third of a series of antityphoid inoculations, given more closely together than the usual three in one week. One regression was associated with a subcutaneous abscess.

CASE 34.—A man aged 24, single, had always had what appeared to be an adequate diet, with no aversions. He was overweight. His first attack, in July 1938, was not anteceded by any discoverable dietary change. His case is described

for two reasons. First, he is the only patient in the series who is known to have improved without question while on a low fat diet prescribed by his family physician. On that regimen, which lasted from September until December 1938, he lost 12 pounds (5.4 Kg.). Second, he had another attack while gradually returning to his usual diet. Although the first of these facts appears to constitute an exception to the general rule, and this may well be the case, it is possible that the reducing diet corrected an imbalance created by a vitamin deficiency, which was again established when he gradually dropped the reducing regimen to return to his normal diet. The figures, obtained from the history, are not accurate enough to answer this question. That such phenomena do occur is widely supposed, and that they can be associated with multiple sclerosis is indicated by cases 14 and 25, reports of which precede this report.

Concerning the remaining patients there are few or no relevant data on episodes of the disease.

## COMMENT

The evidence indicates that many patients with multiple sclerosis have characteristic dietary habits. The majority are poor eaters, the intake being especially poor in visible fat, and particularly in dairy fat. It appears from the findings in this series that a nutritional deficiency exists in some patients and an inadequacy in others.

The question whether the nutritional abnormalities play any significant role in the development of the disease cannot be settled at present. No good evidence has been found which points to a negative answer, but much additional work is needed before an affirmative one is clearly indicated. Some of the evidence from this study not incompatible with an affirmative answer may be stated as follows:

1. The quality of the dietary habits is uniform in groups 1 and 2, and perhaps in group 3.

2. The dietary abnormality is known to have anteceded the onset of the disease in most instances and the first attack in which the patient was seen in all cases. In many cases the disease is known to have been present even prior to the signal symptom.[9a]

3. Attacks occurred in 12 patients after certain changes in food intake.

4. Improvements and remissions have sometimes been associated with increases in food intake or with gain in weight.

5. Except for 6 patients with advanced disease, all did well on a corrected dietary regimen over a fourteen months' period.

6. A correlation between nutritional state and intensity and speed of involvement was observed.

7. Underweight persons did much less well than patients who had normal, or above normal, weights. Many attacks were associated with or preceded by actual loss in weight.

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9a. The very early transient symptom occasionally appearing long before the disease occurs in recognizable form.

8. Numerous attacks also were associated with or preceded by periods of overwork, emotional strain or infection. These are all of a type which may increase caloric and vitamin need and may, therefore, have helped to induce a nutritional deficiency.

It is quite possible that the factors we have enumerated are merely coincidental and have no bearing whatever on the cause of the disease. It is equally possible that they play a role, but only a secondary one—that a nutritional inadequacy coincident with chronic multiple sclerosis may accelerate the progress of the disease, or even precipitate new attacks.

If nutritional deficiency is significant, the data do not indicate clearly whether a single or multiple factors are important. The possibility must also be taken into account that the same etiologic factor may not be present in all the cases which fall into the category of multiple sclerosis. In some cases the disease may be causally connected with nutritional inadequacy and in others not. In addition, it is to be considered that different nutritional substances may be important in different cases.

Most of the patients had been on their characteristic diets for many years without the development of the disease. From this it would seem that if the diet is important, some other factor must enter, such as an infection or overwork, in order to precipitate an attack of multiple sclerosis. It could be argued that the characteristic diets, poor as they often are, are sufficiently well balanced not to create an outspoken vitamin deficiency, which, however, does come on the heels of such events as these.

Another possibility is that nutritional inadequacy and the other factors which antecede so many attacks are important only in lowering the general resistance to infection, and that the disease is the result of an infection which is thus given an opportunity to flourish. Against this possibility is the fact that patients with multiple sclerosis, even when bedridden, seem no more prone to the development of ordinary non-neural infections, including colds, than other people.

Of major importance is the problem why so many patients with multiple sclerosis have an aversion to fats. It is possible that this reflects either a disturbance in lipoid metabolism, perhaps of a nature implied by one of us some years ago or a sensitivity to certain lipoids, such as that postulated by Rivers and his co-workers.[10] Against these possibilities is the fact that the administration of fat in the corrected

10. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39-53, 1933. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, ibid. **61**:689-702, 1935.

dietary regimen has harmed no one, except possibly the 6 patients with advanced disease, and that many of the others have improved under such a regimen. The consideration must also be reckoned with that the heavily involved nervous system may respond differently to the administration of various food items, including fats and vitamins, than does the normal or lightly involved one.

The various questions touched on in this discussion, although necessarily treated speculatively, follow naturally on examination of the data. They were presented also to indicate some of the orientations toward which future research in this and related problems may well be directed. Although the final conclusions are yet to be drawn, much of the material appears to us to be suggestive; it might be worth while to investigate the whole group of obscure degenerative neural diseases from a nutritional standpoint.

SUMMARY

An investigation was made of the lifelong dietary habits of 34 patients with multiple sclerosis. In general, patients with multiple sclerosis are poor eaters, the consumption of visible fat, particularly of dairy fat, being especially poor. In 17 patients (group 1) these defects were quite obvious. In 5 others (group 2) the material gave ground for strong suspicion that the defects existed. In 8 (group 3) there was suggestive, but uncertain, evidence, and in 4 (group 4) there were no signs of abnormality.

Study of the relationship of food intake, weight, intercurrent events and course of the disease suggested a possible connection between nutritional inadequacy and the disease.

Prof. Henry Sherman advised us in the nutritional part of the study.

## DISCUSSION

TRACY J. PUTNAM, New York: I had the privilege of looking over this paper in great detail and should like to say that the brief presentation which Dr. Brickner has given does no justice to the immense wealth of factual material which has gone into its preparation. It represents an enormous amount of work, most thorough and painstaking, as to the dietary habits of a large group of patients with multiple sclerosis, a study that has long been needed. The suggestion that multiple sclerosis is due to dietary deficiency is one that has often been made in recent years; this is perhaps inevitable in these days when any disease of obscure origin is almost sure to be thought to result from vitamin deficiency. Here, however, is something more tangible than any mere theoretic consideration.

To me, the most striking item in Dr. Brickner's data is that the diets of most patients appear to be low in total calories. This furnishes an explanation of the fact which I think all have recognized, that the patients with multiple sclerosis are apt to be thin, as Dr. Brickner has pointed out. Are they thin because they have multiple sclerosis, or are they thin because they take a low caloric diet, which is also associated with the onset of multiple sclerosis? This is not wholly clear

from the data, although, as Dr. Brickner points out, the low diets appear to have been taken in many instances over a long period before the onset of the disease.

It would seem quite possible that by the time the disease is established the patient's actual caloric requirements are decreased on account of muscular weakness. The effect of neurologic diseases on caloric requirements has not been thoroughly studied. If one assumes the patient's caloric needs have been satisfied by his intake, the diets in Dr. Brickner's tables do not seem grossly abnormal. They do seem to be rather higher in protein and rather lower in fat than some control diets. But the control diets usually selected are those of paupers on relief, which are planned to get the utmost caloric value out of a given budget, while these patients are, I take it, in a slightly better average economic status, which usually involves a somewhat higher level of protein in the diet. The diets are, I should say, on the average fairly typical reducing diets, such as many people eat by choice, at least in part. It is obvious that there is no question of any deficiency in protein or in carbohydrate. The fat content is not extremely low, not nearly so low as the average in some countries—in Germany during the late war, in China or in Africa. Although, as Dr. Brickner points out, there is some deficiency in intake of butter, cream is consumed by most of the patients in moderate amounts, which would seem to compensate for the inadequate use of butter. It seems to me, moreover, that the diets do not give any clear evidence of a deficiency in vitamins, certainly not of the B complex, which is pretty well represented. As he has pointed out, it is difficult to be sure what represents an adequate level of the others.

Dr. Brickner is to be congratulated on this careful piece of work, and most of all, it seems to me, on the conservatism of the conclusions he has drawn from it. If a dietary deficiency is an important link in the causation of multiple sclerosis, a change in diet should guard against relapses, and a fair number of cases followed over a reasonable length of time should clearly show whether it does or not. I may say that my own experiences with the use of individual vitamins have been most discouraging.

NORMAN JOLLIFFE, New York: I wish to compliment Dr. Brickner on being able to collect and tabulate an extensive mass of data and then having the courage to discard most of it. He found that the dietary histories of patients can be analyzed, with profit, only qualitatively.

There are two points in Dr. Brickner's presentation that I should like to emphasize, since both seem to indicate that nutrition may play some role in the multiple sclerosis syndrome. The first is that of 35 patients only 4 gave a history of a definitely adequate diet. This is more important than to say that 31 were possibly on an inadequate diet. About two years ago I pointed out that a patient who can tell in detail what he has eaten is probably on a diet that is inadequate in some respect. It is only people who are food cranks or people who are placed on menus rather than diets who are able to remember what they ate yesterday, the day before, two weeks ago, two months ago or last year. An unusually large number of Dr. Brickner's patients were able to give in detail their past dietary history. In addition, these statements as given by the patients were corroborated by their friends and their relatives.

The second point I should like to emphasize is that this syndrome, multiple sclerosis, is characterized in most patients by remissions. Many of the recognized nutritional deficiency diseases are also characterized by remissions: Pernicious anemia, pellagra and scurvy are examples.

WARDNER D. AYER, Syracuse, N. Y.: I should like to ask Dr. Brickner whether he considers that there might be significance in the rather striking geographic distribution of this disease.

In the Orient, especially in Japan and China, multiple sclerosis is unknown. Certainly, there they have restricted diets in the fullest sense; if I recall correctly, the highest peak of incidence of the disease is in Switzerland and the second highest in Scandinavia, where it is believed the people have been best fed, especially in fats.

FOSTER KENNEDY, New York: Perhaps Dr. Brickner might be interested in hearing that thirty years ago, when I was a medical officer in the National Hospital in London, where, as everybody knows, there is a very high incidence of multiple sclerosis, it was routine to give all patients with multiple sclerosis a high fat diet. I do not believe the rationale was ever worked out in a scientific fashion, nor do I believe that dietary deficiency came into the picture as something to be corrected. It was an entirely empiric therapeutic procedure, based on a vague idea that, the fatty sheaths being degenerated, it was necessary to supply fat. But as a routine all patients with multiple sclerosis was given a high fat diet, with extra cream and extra quantities of butter.

RICHARD M. BRICKNER, New York: Dr. Putnam suggested that the low dietary intake was perhaps due to the weakness of the patients. The implication was that under such conditions a patient's caloric need may go down. As I pointed out, most of our patients were not so weak but that they were still able to work; also, a number of them were having real remissions and were symptom free. I think that one would expect, if a patient has a reduced capacity and still does a full day's work, that his caloric requirement should be higher, not lower, than usual.

I wish to stress that many of these persons will not eat fats. One patient said, "Well, if my future depends on butter, I will resign myself to my fate." That is the way they feel about it. Their diets are low in those materials, as will be seen in the paper which contains many corroborative details.

I agree thoroughly with Dr. Jolliffe's suggestion that the best way to study the question further is to see how many relapses can be prevented. All know that evaluations of therapy, perhaps, especially in the case of multiple sclerosis, are extremely difficult. I think the only way to be sure at all is to observe how many patients fail to regress, rather than how many improve. That is one reason we have obtained a bit of encouragement from our observations in the last fourteen months. No patient, so far, who has adhered to the prescribed dietary regimen has regressed.

The absence of the disease in Oriental peoples and in African natives is, of course, of great interest. I have always thought that the freedom of those people from multiple sclerosis, whatever the cause of the disease may be, is racial. It is known, for instance, that Negroes in this country do not get the disease commonly; I have seen only 2 such instances.

With regard to Dr. Jolliffe's comments on conservatism, I should rather present anything connected with this disease in the most conservative terms of which I can think. This disease is a will-o'-the-wisp, and the pursuit of it is that of a will-o'-the-wisp. It seems to be impossible to drop it if you once start it, and I, although I have never had multiple sclerosis, suffer from it. As a result, I have chosen the most conservative possible terms in which to state this whole case, although I am convinced that the facts I have reported are true. I am very

much interested in the remarks made by Dr. Kennedy about his early experience in London, and I wonder if those patients did well when they were given proper nourishment.

FOSTER KENNEDY, New York: They were thought to do better. It was the routine, the rule of the house, one of those house rules that grows up as a result of experience; but it was never scientifically evaluated.

JOHANNES M. NIELSEN, Los Angeles: I should like to remark that one of the most interesting patients with multiple sclerosis that I have ever had acquired the disease after living in China for twenty years.

FOSTER KENNEDY, New York: A white person?

JOHANNES M. NIELSEN, Los Angeles: A missionary who lived in China for twenty years and then became ill with multiple sclerosis came to this country and died of it after fifteen years of illness; the diagnosis was verified post mortem.

# LINDAU–von HIPPEL DISEASE

## A REPORT OF FOUR CASES

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According to Cushing and Bailey,[1] Schuback was the first to refer to angiomatosis of the central nervous system as Lindau's disease. Lindau,[2] in studying angiomatous nodules in cerebellar cysts, observed an association of this lesion with angiomatosis of the retina, otherwise known as von Hippel's disease, and by studying the reported cases of the latter disease he noted that it was not unusual to find a coincidental hemangioma of the cerebellum or of some other part of the nervous system (Lindau's disease). He considered it possible that the hemangioma of the cerebellum was only part of a systemic angioblastic disorder of the central nervous system often associated with a cystic pancreas, cystic kidneys and, more rarely, hypernephromas, tumors of the epididymis and angiomatosis of the liver. However, the abdominal lesions are not known to cause symptoms. The complete complex is rare.

Lindau's conception represents a newly recognized disorder, probably of congenital origin and due to maldevelopment of the mesoderm in the third fetal month. This suggestion explains the prevalence of

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Read at the meeting of the American Neurological Association, Atlantic City, N. J., June 8, 1939.

From the Section on Neurologic Surgery (Dr. Craig), the Section on Ophthalmology (Dr. Wagener) and the Section on Pathologic Anatomy (Dr. Kernohan), the Mayo Clinic.

* The term "Lindau–von Hippel disease" was selected because of the association of the retinal lesion with lesions of the brain and other organs of the body. In view of the fact that Collins was the first to describe retinal angiomatosis, we might have called it "Lindau-Collins Disease."

1. Cushing, H., and Bailey, P.: Tumors Arising from the Blood-Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

2. Lindau, A., in Discussion on Vascular Tumours of the Brain and Spinal Cord, Proc. Roy. Soc. Med. (Sect. Neurol. & Sect. Ophth.) **24**:363-370 (Jan.) 1931.

hemangioblastomas in the posterior fossa; for at that stage of development there is in this region a very rich capillary network which forms the choroidal tufts of the fourth ventricle. In considering the genesis of the cysts, Lindau assumed that the contents are produced by some exudative function. Cushing,[1] however, expressed the opinion that the fluid is a transudate, derived from the tumor and not from the wall of the cyst, an opinion borne out by the fact that removal of the nodule of tumor prevents reformation of the cyst.

Twenty per cent of the cases of angiomatous cysts have been observed to be familial; case histories have reported the occurrence of such cysts in 3 generations. A preoperative clinical diagnosis of a cerebellar hemangioblastoma is possible from a demonstration of a retinal angioma, a familial history or both.

Cushing [1] has pointed out that the syndrome of an angiomatous tumor of the cerebellum does not differ from that of a cerebellar tumor of any other type and that only when there is an associated angioma of the retina can the diagnosis of hemangioblastoma of the cerebellum be suggested before operation. The ages of patients who have such tumors are greater than those of patients who have tumors of other types, and the progress of the symptoms is slower.

According to Riddoch,[3] the clinical picture of Lindau's disease usually begins with paroxysmal headache, which occurs on waking or is brought on by stooping, coughing or sneezing. The attacks may be long or short. The pain, which is suboccipital, frontal, temporal or general, is described as aching or shooting. It may be associated with vomiting, with or without nausea, but this symptom may be late in making an appearance. The intermittent attacks of headache, between which the patient may be perfectly well for months, are undoubtedly due to intermittent hydrocephalus. The intermittency and briefness of the attacks of hydrocephalus in the earlier stages of the complaint account for the prolonged absence of papilledema. The optic disks may be normal for months after the onset of the headaches, and this long interval is one of the striking features of the clinical picture.

Prominent cerebellar symptoms and signs are usually delayed, although giddiness may come early in the development of the headache. The first indications of a cerebellar disorder are a stiff attitude of the head, unsteadiness in walking and turning and slight hypotonia with clumsiness of the fingers, usually unilateral or more prominent on one side than on the other. Its customary occurrence in the second, third

3. Riddoch, G., in Discussion on Vascular Tumours of the Brain and Spinal Cord, Proc. Roy. Soc. Med. (Sect. Neurol. & Sect. Ophth.) **24**:382-383 (Jan.) 1931.

and fourth decades, the long history of intermittent headaches of the hydrocephalic type, the late appearance of papilledema and cerebellar signs and the associated angioma of the retina (if present) are the important diagnostic signs.

There are many cases of Lindau-von Hippel disease in which the syndrome is incomplete.[4] We have encountered many cases of hemangioma of the cerebellum in which hemangioma of the retina was not present. We have examined 1 case in which there was a cyst of the cerebellum with a small hemangioma in the wall. The cyst was associated with syringomyelia and hemangioma of the spinal cord, polycystic pancreas and polycystic kidneys and liver, but hemangioma of the retina was not present. We have encountered several cases of typical hemangioblastoma of the spinal cord in which no other lesion was clinically demonstrable. We have observed at necropsy several instances of polycystic pancreas, liver and kidneys in which no lesion was present in the central nervous system or the eyes.

In the 4 cases of hemangioblastoma of the cerebellum reported here, angiomatous lesions of the retina were present, and in all 4 instances operation was performed. Three of the 4 patients are living; one, seven years; one, one and a half years, and one, six months after operation. The other patient did not survive, and in this case the pathologic study was very interesting because the observations conformed to Lindau's conception of the disease.

From the ophthalmoscopic standpoint, these cases represent four distinct phases of the disease. In 1 case the onset and development of the retinal lesion were very atypical. In another the lesion was confined to one eye, and papilledema was not present. In the 2 remaining cases angiomas were present in both retinas. In 1 instance, however, the angioma in one eye was very small and had not developed fully into a large tumor. It had undergone almost complete gliosis. In the last case the angioma in the second eye had resulted in detachment of the retina and formation of a secondary cataract; papilledema was also present.

According to Cushing and Bailey,[1] the first authentic case of angiomatosis of the retina was reported by Fuchs in 1882; the first histologic description was made by Collins[5] in 1894, and the first

4. Davison, C.; Brock, S., and Dyke, C. G.: Retinal and Central Nervous Hemangioblastomatosis with Visceral Changes (von Hippel-Lindau's Disease), Bull. Neurol. Inst. New York **5**:72-93 (Aug.) 1936. Russell, D. S.: Capillary Haemangioma of Spinal Cord Associated with Syringomyelia, J. Path. & Bact. **35**:103-112, 1932. Wolf, A., and Wilens, S. L.: Multiple Hemangioblastomas of the Spinal Cord with Syringomyelia: A Case of Lindau's Disease, Am. J. Path. **10**:545-567 (July) 1934.

5. Collins, E. T., in Discussion on Vascular Tumors of the Brain and Spinal Cord, Proc. Roy. Soc. Med. (Sect. Neurol. & Sect. Ophth.) **24**:372-381 (Jan.) 1931.

association of angioma of the cerebellum with angioma of the retina was noted by Seidel.[6] The lesion in the retina was described by Fuchs as an arteriovenous aneurysm. The typical uncomplicated angioma of the retina is easily recognized clinically and is always suggestive of an arteriovenous aneurysm. The characteristic ophthalmoscopic picture is that of a greatly dilated artery, often beaded in appearance in its proximal portion near the disk and terminating distally in a somewhat round reddish angiomatous mass, usually situated in the extreme periphery of the retina. From this mass a greatly dilated vein returns to the optic disk in a variable course somewhat parallel to that of the dilated artery. Since there is often free communication between arterial and venous blood in the angioma, the blood in the dilated artery may be almost the same color as that in the vein.

Because the peripheral angioma in its later phases has a tendency to cause transudation and the formation of cysts, it may be considerably obscured by the surrounding subretinal and retinal edema and exudation. In some cases these may be of sufficient amount to cause localized or generalized detachment of the retina. Hemorrhage, as a rule, is rather scanty. In typical cases, however, the enlarged pair of blood vessels is always striking, even in the later phases of the lesion; if their course is followed carefully to their point of junction, the network of capillaries can usually be at least dimly defined.

Authors who consider these angiomas to be of congenital origin ascribe the changes visible in the retina to the gradual enlargement of the tumor, the resultant interference with the circulation in the communicating vessels and the gradual increase of exudation in and degeneration of the surrounding retina. It is recognized also that a small angiomatous lesion in the retina may not increase in size and may be recognized ophthalmoscopically only by the presence of a small glioma with delicate arteriovenous communications.

From the ophthalmoscopic standpoint, however, it is by no means certain that the lesion in all cases develops from the increase in size of a congenitally present angioma. In some instances it is possible in the early stages to observe changes in the peripheral portions of the retinal arteries and veins which cannot be distinguished readily from arteritis and phlebitis. Definite formation of a tumor and an arteriovenous communication may not occur for several years after the first changes have been noted. Von Hippel's [7] first case would appear to have been of this type. The possibility of the lesion's developing visibly in this manner may account for its late recognition in certain instances, such as the first case in this report.

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6. Seidel, cited by Cushing and Bailey.[1]

7. von Hippel, E., cited by Cushing and Bailey.[1]

It is certain that as the lesion advances, angioma-like changes may develop in vessels which when the original typical angioma was discerned did not appear to be involved. Frequently, exudative and degenerative changes are found in the retina at a considerable distance from the part supplied or drained by the dilated vessels which terminate or originate in the localized angioma. On the other hand, cases are encountered in which ophthalmoscopy discloses diffuse dilation of all the retinal vessels with resultant edema and exudation but without the formation of a definite localized angioma. A somewhat similar diffuse dilation of the vessels may be seen on the surface of the cerebellum in the neighborhood of an angiomatous cyst. These facts suggest that the disease known as angiomatosis may at times involve the vessels in a rather diffuse manner and that the development of a localized angioma may be a late, rather than an early, feature of the disease. It is obvious, however, that the basic lesion must be some congenital defect in the vascular structures.

The surgical treatment of the cerebellar lesion is drainage, removal of the tumor nodule and when possible removal of the entire wall of the cyst. Dandy [8] has stated that extirpation of the solid angiomatous nodule should be attended with a minimum of danger and leave the patient permanently cured without after-effects. Simple evacuation of the cyst, the application of fixative fluids to the walls of the cyst and roentgen therapy without removal of the tumor will be followed by recurrence.

From the clinical point of view, these 4 cases represent distinct problems in diagnosis. Case 1 was the most difficult because of the paucity of neurologic findings.

## REPORT OF CASES

Case 1.—A woman aged 42 years related a long history of headaches, which were confined to the left side and had occurred intermittently. Apparently they had been relieved by drainage of the sinuses. For eleven years she had complained of progressive loss of vision of the right eye.

About a year before, the patient noticed for the first time an unsteady gait, which lasted three weeks, disappeared completely and recurred six months later. With the onset of the unsteady gait, the headaches became aggravated. The headaches then began to occur in severe attacks, frequently at night or in the early morning and lasted from a half-hour to one and one-half hours. They were accentuated by motion or straining, and frequently opiates were required for relief.

By the time difficulty in walking became permanent, the patient's vision was severely impaired; diplopia appeared on several occasions. Simultaneously, the patient suffered from several attacks of projectile vomiting. Examination of the eyes revealed a lesion in the lower peripheral portion of the right retina. It

8. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, pp. 1-682.

appeared to be tuberculous, and proliferating bands had formed with a resultant irregular detachment of the lower portion of the retina. In addition, both disks were edematous, the right being elevated 2 D. and the left less than 1 D.

Because of the severe headaches, repeated spinal punctures were done, and considerable relief resulted. Since the pressure of the spinal fluid was found to be somewhat high, encephalography was carried out. The roentgenograms, however, did not reveal evidence of an intracranial lesion. A regimen of dehydration was instituted in conjunction with repeated spinal punctures.

A little more than a year after the first symptoms occurred, attacks of dizziness began, brought on by sitting up or lying down quickly and lasting about ten minutes. Slight incoordination of the left arm and leg followed, and it was noticed that the patient staggered from side to side and had a tendency to fall

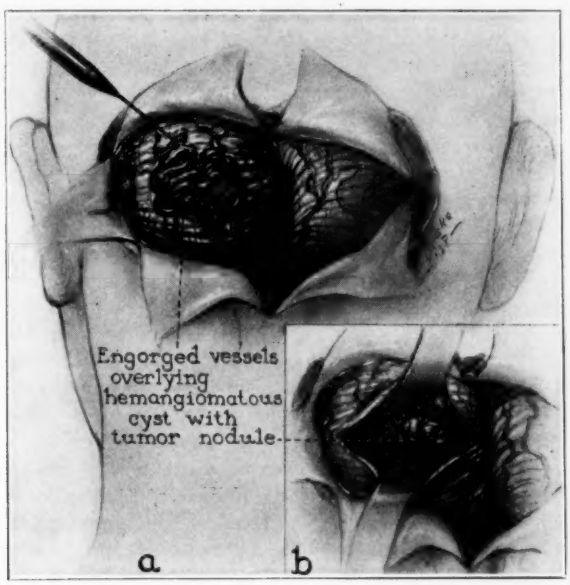


Fig. 1 (case 1).—Drawing of cerebellum revealing engorged cortical vessels, cystic cavity and tumor nodule.

forward. Ataxia of both hands developed, and the vision of the left eye began to fail.

At this time a neurologic examination revealed mild dysmetria and ataxia of the right upper extremity. The deep reflexes in both upper extremities were active and equal. In the lower extremities, the reflexes were diminished on the right. The abdominal reflexes were absent. When the patient gazed laterally toward the right, nystagmus was present. Ophthalmoscopic examination revealed choked disks with elevation of 4 D. on the right and 5 D. on the left. Proliferating retinitis with detachment of the lower portion of the retina was still present in the right eye. It was the enlarged vessels of the lower portion of the retina and the marked vascularity of the underlying lesion that first aroused the suspicion that it might be angioma, although a definite tumor mass could not be made out. Examination of the visual fields revealed in the right eye a superior altitudinal

and temporal anopia with a central scotoma and in the left a relative contraction of the upper nasal portion of the field of vision. It was questionable whether these defects were due to the local lesions in the optic nerve and retina or whether they represented, in part at least, a relative right homonymous hemianopia.

The results of the neurologic examination and, in addition, the progress of the symptoms indicated a lesion probably situated in the posterior fossa. However, because of the questionable changes in the visual fields, ventriculograms were made; these showed a dilated ventricular system, indicating that a lesion existed inferior to the tentorium. Through an opening made by suboccipital craniotomy the left cerebellar tonsil was seen herniated below the level of the first cervical vertebra with associated broadening and flattening of the convolutions. The entire cortex was covered with large engorged and tortuous vessels. A blunt needle inserted in the left cerebellar hemisphere encountered a cyst. A few cubic centimeters of yellow fluid was removed, which coagulated on standing. After the vessels on the surface of the cerebellum had been ligated and coagulated, an incision was made into the cyst. A mural nodule lying on the mesial wall was dissected and completely removed together with the lining of the cyst (fig. 1).

On microscopic examination, the tumor, which weighed 5 Gm. and measured 3 by 2 by 2.5 cm., proved to be a hemangioblastoma. Histologic examination of the tissue showed that it contained more large thin-walled blood spaces than are usually seen in hemangioblastomas. There were regions in which numerous small blood spaces were lined by endothelial cells, some of which were swollen and contained vacuoles that gave the cells a typical foamy appearance. There were, however, more foam cells between the blood spaces than actually lined the spaces.

Staining showed the vacuoles of the foam cells to contain fat. The relationship of the xanthic cells to the walls of the blood spaces was best demonstrated with a combination of Perdrau's silver impregnation method for connective tissue and scarlet red staining for fat. The relationship was also well brought out with the Mallory-Heidenhain stain. This stain showed the relationship better than the Mallory phosphotungstic acid–hematoxylin stain.

After the operation the patient was immediately relieved of headaches, vomiting and diplopia. Her recovery was gradual and in three or four weeks she could walk without difficulty, and the papilledema had receded. The visual fields were normal except for the central and altitudinal defect due to the local lesion in the right retina. A recent examination revealed that papilledema was not present and that vision was normal except for the retinal lesion of the right eye.

The next case represented a much easier problem than the first. The history of vomiting, headache, dizziness and hiccups with nystagmus and incoordination was definitely suggestive of a lesion in the posterior fossa. The angiomatous lesion in the retina was an indication of the nature of the tumor in the cerebellum.[9]

Case 2.—A man aged 26 years was well until five months previous to his examination at the clinic. His symptoms at the time of onset consisted of occipital headaches which extended forward to the left frontotemporal region and in two to three months had progressed forward into the frontal region. One month prior to registration at the clinic, he began to have vomiting associated with nausea and vertigo. He stated that he had been nauseated daily and had begun to stagger,

9. The operation was performed by Prof. J. R. Learmonth of Edinburgh, Scotland, while he was a member of the Mayo Clinic staff.

that his head "went around in circles," and that he had begun to vomit. Severe episodes of hiccups had occurred during the previous three months. One month before examination, numbness of his entire left side began to develop.

The examination of the eyes revealed visual acuity of 6/4 in the left eye and 6/7 in the right eye. Ophthalmoscopic examination discovered no abnormalities in the right eye. In the left eye a pair of typically enlarged vessels led from the lower margin of the optic disk to a definite angioma in the lower portion of the

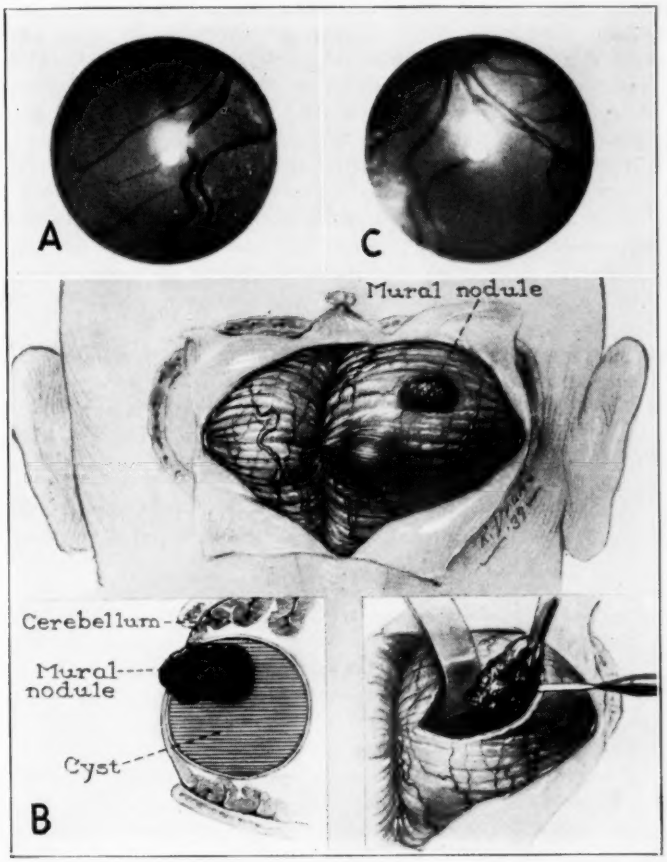


Fig. 2 (case 2).—*A*, photograph of a retina of the left eye before the operation on the cerebellum. The dilated retinal artery and vein lead to the angioma in the lower peripheral portion of the retina. *B*, drawing showing cortical cerebellar tumor with associated cyst and its removal. *C*, photograph of the retina. The same artery and vein as in *A* three years after the operation on the cerebellum. Some of the exudative changes in the neighboring retina can be seen.

periphery of the retina. There were massive exudation in the surrounding retina and mild detachment of the periphery of the retina (fig. 2 *A*). The neurologic examination showed generalized weakness, bilateral incoordination of the upper

and lower extremities, a positive Romberg sign and marked bilateral nystagmus. The history and the results of examination were suggestive of a cerebellar lesion, and in considering the angiomatous retina we suspected a hemangioblastoma.

At operation, the right cerebellar lobe was observed to be larger than the left. The convolutions were broadened and flattened, especially toward the vermis where a bluish discoloration was suggestive of a cyst. At the middle of the posterior and upper aspects of the right cerebellar lobe, a nodular cystic hemangioma about 3 cm. in diameter could be seen in the cortex. The vessels leading to this nodule were ligated. The cyst was opened and was found to extend well toward the midline (fig. 2 *B*). The tumor was completely removed. On microscopic examination, we observed that this neoplasm took the scarlet red stain; the tissue seemed to consist almost entirely of fat. However, on examination of sections impregnated by the Perdrau silver stain for connective tissue, it was identified as a typical hemangioblastoma. On combining the two aforementioned methods, we noted that most of the fat was in large foam cells between the blood spaces. The Perdrau method showed us the characteristic manner in which the small blood vessels extended at right angles from the walls of the larger blood vessels and the free anastomosis present between the smaller blood spaces.

After operation, the nystagmus disappeared, and the vision improved. The eye was given three courses of radiotherapy in an attempt to reduce the size of the retinal angioma.

Three years after operation the patient returned for examination. The 2 large vessels emerging from the lower border of the optic disk were still present and led down to the site of the angioma, which now, however, appeared to be largely scar tissue with atrophy and degeneration of the surrounding retina (fig. 2 *C*). The patient's general condition was excellent.

The next case also presented a comparatively simple diagnostic problem, and the type of tumor was indicated by the angioma in the retina.

Case 3.—A woman aged 52 years complained of vomiting which had persisted for seven months. Associated with the vomiting was a bursting sensation at the vertex of the skull. This sensation, beginning in the morning and lasting all day, occurred every other day and was associated with some blurring of vision and dizziness as well as episodes of diplopia.

Her head was bent forward, and the neck was stiff. The results of neurologic examination were essentially negative except for an ataxic gait. Ophthalmoscopic examination showed in the right retina a typical angioma occupying the peripheral part of the superior temporal quadrant; the characteristically dilated vein and the dilated and beaded artery were also present (fig. 3 *A*). The angioma was clearly outlined, with only a small amount of exudation in the surrounding retina. In the superior temporal quadrant of the left retina, about 4 to 5 disk diameters from the margin of the optic disk was a small angioma. In this there was a definite communication between a small artery and a vein, but proliferation of glial tissue had occurred rather than the formation of an angiomatous cyst (fig. 3 *B*). The pupils were normal in size, shape, position and reflex activity to light; there was, however, some diminution of response to accommodation. The external ocular movements were normal; nystagmus was not present. Vision in each eye was 6/6 with the proper refractive correction, and the central and peripheral portions of the fields of vision were normal. Roentgenologic examination of the

skull gave negative results. The presence of a tumor of the cerebellum, angiomatous in nature, was suspected.

At operation, the dura over the posterior fossa was tense despite the absence of papilledema. After the posterior horn of the left lateral ventricle was drained to relieve the intracranial tension, the dura was opened, revealing a collection of tortuous vessels on the surface of the left cerebellar lobe. The right cerebellar lobe appeared normal. A cyst in the left cerebellar lobe was drained of 5 cc. of

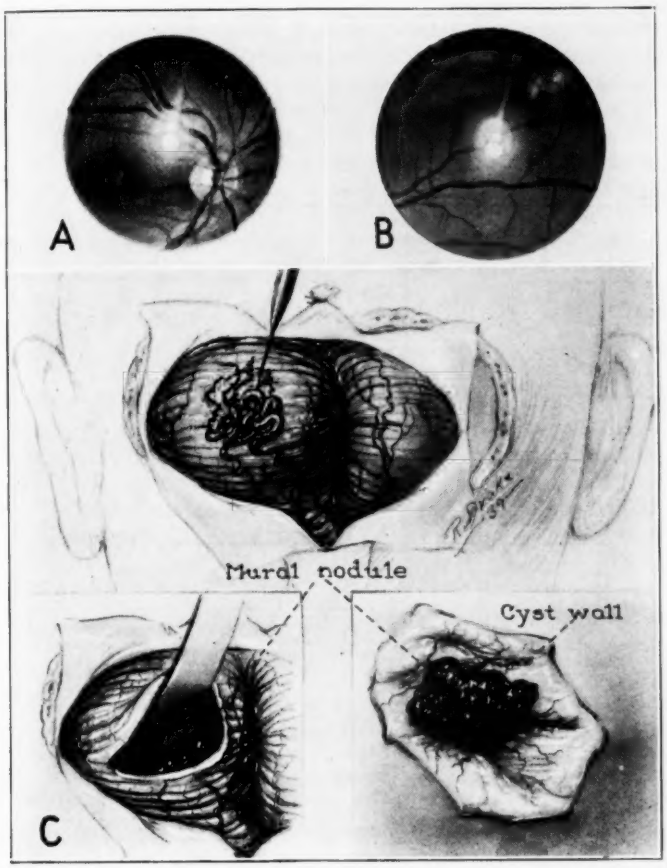


Fig. 3 (case 3).—*A*, photograph of the retina of the right eye. The dilated retinal artery and vein lead to the angioma in the superior temporal peripheral portion of the retina. *B*, photograph of the retina of the left eye; a small angioma is present in the superior temporal quadrant of the retina. *C*, drawing of cortical vessels, tumor nodule and resected tumor with cyst wall.

yellow fluid, which coagulated on standing. The cyst, which was 5 cm. in diameter and which occupied the upper and outer portion of the left cerebellar lobe, was opened and removed together with the entire wall of the cyst (fig. 3*C*).

Microscopically, the tumor proved to be a typical hemangioblastoma, which, on routine staining, was observed to contain an excessive number of foam cells. When the tissue was prepared by a combination of scarlet red staining for fat and Perdrau's silver impregnation method for connective tissue, most of the foam cells were found to be within the lumens of the blood spaces, which seem to be obstructed by these swollen cells. There were also large numbers of foam cells between the blood spaces. It is unusual to find more foam cells in an intravascular position than in an extravascular site.

Convalescence was uneventful, and the neurologic reexamination at dismissal revealed only slight ataxia, astereognosis and generalized muscular weakness. On the patient's return home her condition gradually improved, and six months later she was doing all of her own housework.

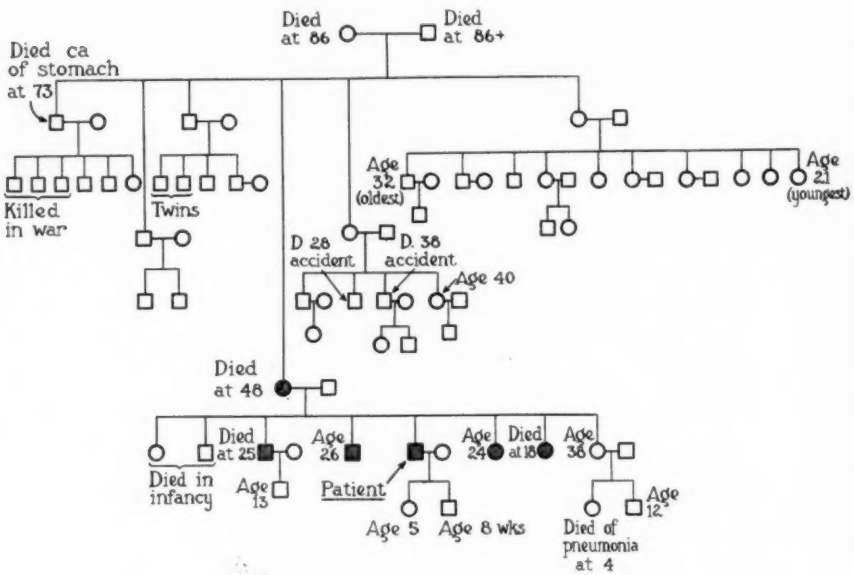


Fig. 4 (case 4).—Genealogic chart.

The next case (case 4) is the most interesting of the 4 because of the long history and the progression of the disease. The papilledema and the early history of unsteadiness of gait due to herniation of the tumor through the foramen magnum were overshadowed by the cerebellar signs. The genealogic chart is interesting (fig. 4).

CASE 4.—A man aged 32 years complained of pain in the back of the neck. This pain had been present for five or six years, and some unsteadiness of gait had persisted for two years.

The family history proved to be interesting. The patient's father was old, but his mother died at the age of 48 years after suffering from pain in the neck for six years and from paralysis of both arms for six months before death. She had been blind in one eye for several years. One older brother died of a brain tumor

at the age of 25 years, having suffered from severe pain in the neck and from trouble with his eyes for several months. Another brother had died at the age of 26 years. A younger sister had been examined at the clinic in 1925, and an angioma had been found in the retina on ophthalmologic examination. This sister had died at the age of 18 years, having suffered from pain in the neck for six months.

Five or six years before examination the patient noticed the onset of sharp pains in the back of the neck associated with impairment of sensation in the hands. Both the pain in the neck and the impairment of sensation had progressed gradually. For five years there had been pain in the left upper portion of the thorax; the severity of the pain increased on coughing. Four years before registration he went to an oculist, who discovered that the patient was completely blind in the left eye. For two years there was progressive unsteadiness of gait.

The patient was emaciated and slightly cyanotic, and the neck was rigid. The face was directed downward and to the left. A severe ataxia and incoordination of all the extremities were present; these became much worse when the eyes were closed. Vibration sense was absent over the entire body. Joint sense was absent in the hands and diminished in the toes. Astereognosis was severe in both hands. The sense of touch was moderately diminished, and the sense of pain and of temperature was slightly diminished in the forearms and hands. Muscular strength was very slightly diminished in the upper limbs but elsewhere was normal. There was generalized hyperreflexia, but signs of involvement of the pyramidal tract were not present.

Ophthalmologic examination showed that the visual acuity of the right eye was 6/30. There was a mature cataract in the left eye, which made funduscopic examination impossible. The right fundus had papilledema of 6 D. The superior temporal artery and vein of the retina were greatly dilated and led out to an angioma elevated about 8 D. and surrounded by a large region of edema of the retina (fig. 5*A*). This retinal picture was considered typical of Lindau–von Hippel disease. The visual field of the right eye was normal except for enlargement of the blindspot.

The examination indicated a hemangiomatous lesion on the posterior surface of the cervical portion of the spinal cord near the foramen magnum with intracranial extension compressing the nuclei of Goll and Burdach.

On a suboccipital craniotomy and laminectomy of the upper cervical portion of the spinal cord we observed a large hemangioma which completely filled the fourth ventricle and posterior cistern and involved the pons and medulla oblongata and the upper cervical portion of the spinal cord (fig. 5*B*). By gentle dissection and the use of electrosurgical coagulation and silver clips the hemangiomatous mass, which measured about 4 cm. in diameter, was dissected free. There was a cyst in the upper part of the cervical cord, and a midline incision was made to relieve the pressure. Although the patient's condition remained unchanged during the operation, he expired twelve hours afterward.

At necropsy there was no evidence of the tumor in the fourth ventricle. However, another tumor, measuring 3 by 4 cm., was discovered in the right hemisphere of the cerebellum; it was a solid granular mass with a small cyst situated in the middle. It was embedded in the hemisphere, not connected with the fourth ventricle or the meninges, sharply circumscribed but not encapsulated. There was an internal hydrocephalus of the lateral ventricles, third ventricle and anterior half of the fourth ventricle as well as compression of the pituitary gland and flattening of the convolutions of the cerebral hemispheres. The medulla oblongata and the entire spinal cord were much larger than normal. Cross section showed

syringobulbia and syringomyelia extending from the upper end of the medulla oblongata to the sacral portion of the spinal cord. In the upper lumbar region of the spinal medulla the cavity that was caused by syringomyelia, however, was replaced by a tumor mass about 2 inches (5.08 cm.) in length, the cavitation being present, however, both above and below the tumor (fig. 6).

In the retina of the right eye there was a small hemangioma, about 1.5 mm. in diameter, in the superior temporal quadrant near the ciliary body. A large tortuous

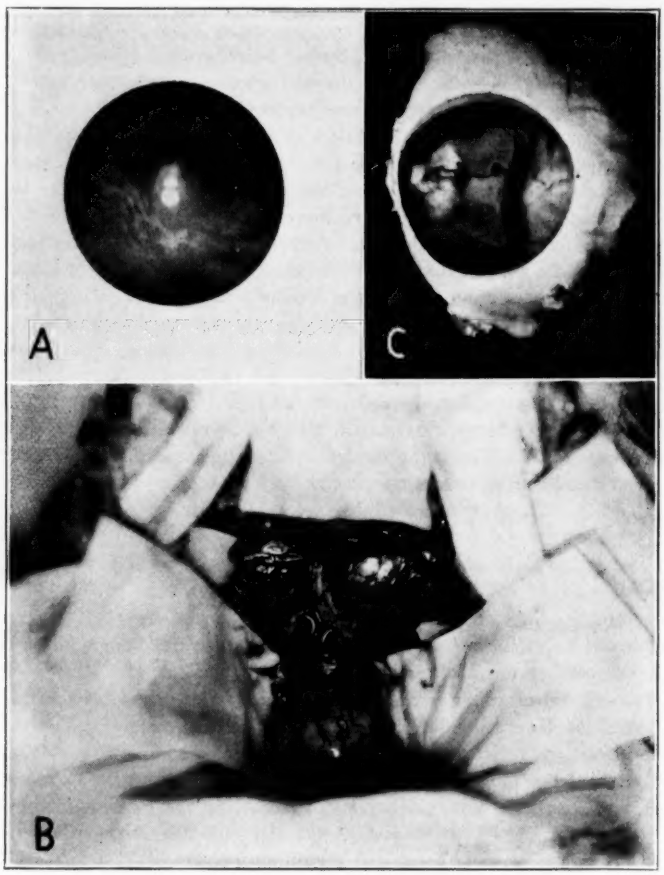


Fig. 5 (case 4).—*A*, photograph of the retina of the right eye. The dilated artery and vein are shown in the edematous retina in the neighborhood of the angioma in the superior temporal peripheral portion of the retina. *B*, photograph taken at the operating table; the angiomatous mass fills the fourth ventricle. *C*, photograph of the posterior half of the right eye; the 2 dilated vessels extended from the optic disk to the small tumor, which is surrounded by edema, exudate and gliosis.

vessel extended from the optic disk to this small tumor (fig. 5 *C*). There was an opacity of the lens of the left eye, and on sectioning this eye we found a complete

detachment of the retina which formed a solid strand of tissue about 4 mm. in diameter extending from the optic disk to the posterior surface of the lens. From this point it spread outward, covering the lens and extending to the posterior margin of the ciliary body, to which it was attached. The fluid between the detached retina and the choroid was yellowish and contained numerous cholesterol crystals. Resting on the posterior surface of the lens on the nasal side of the eye there was a small vascular tumor, about 5 mm. in diameter, into which 2 large blood vessels entered from the axial mass of detached and fused retina.

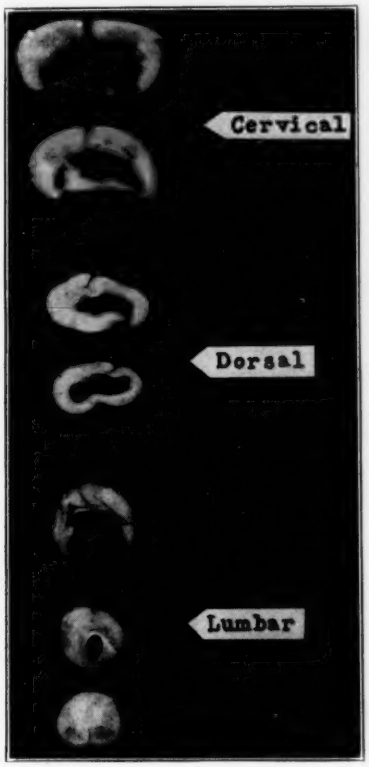


Fig. 6 (case 4).—Photograph of spinal cord showing the intramedullary hemangioblastoma in the upper lumbar segments, associated with syringomyelia proximal and distal to the neoplasm.

Numerous cysts, varying from less than 1 mm. to 1 cm. in diameter, were present throughout the pancreas. There were numerous cysts of both kidneys, and in addition there were many small adenomas in the cortex of each kidney. There was a cyst 4 mm. in diameter in the liver. The spleen was normal. Meckel's diverticulum was present, and also a small adenoma of the left epididymis.

The tumor removed was a typical hemangioblastoma such as is usually encountered in Lindau–von Hippel disease. There were numerous large dilated thin-walled blood vessels with numerous small branches. The outlines of the smaller blood

spaces were best seen when stained by Perdrau's silver impregnation technic. The endothelial cells that lined the terminal blood spaces were swollen and had obliterated the lumen so that the silver method was necessary to demonstrate the outlines of these spaces. There were numerous swollen endothelial cells laden with lipoid between the capillaries. These fat-laden cells were beautifully demonstrated with the scarlet red stain. The relation of the fat-laden endothelial cells to the walls of the blood spaces was brought out well by a combination of scarlet red staining and Perdrau's silver impregnation. Many of these cells lined the blood spaces, but there were also large numbers situated extravascularly. The tumor in the lumbar

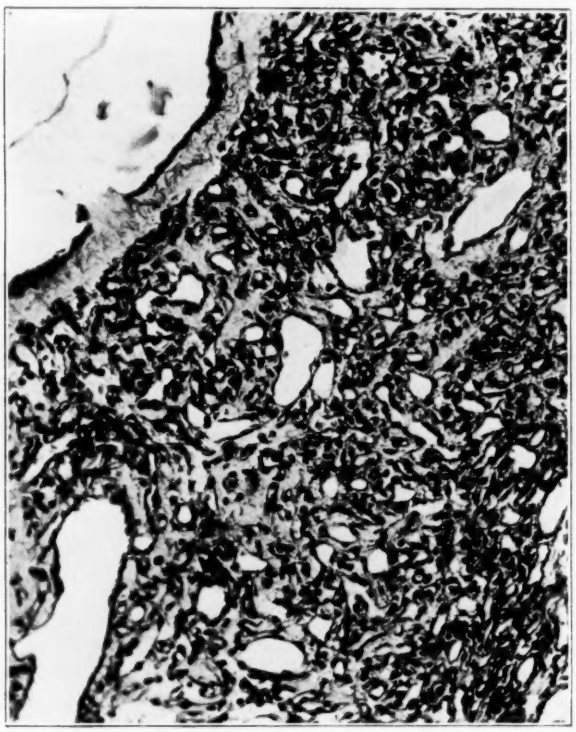

Fig. 7 (case 4).—Photomicrograph of the intramedullary hemangioblastoma. This is typical, with large and small blood spaces lined by endothelial cells. Similar cells can be seen between the blood spaces. (Hematoxylin and eosin stain; × 165).

portion of the spinal cord was similar to that removed from the fourth ventricle (fig. 7).

As is common in hemangioblastomas in the substance of the spinal cord as well as in those in the cerebellum, there was a sharp line of demarcation between the neoplasm and the surrounding structures of the cord. The histologic picture of the syringomyelic cavity was characteristic of this condition. The walls consisted of dense glial tissue, which in places was lightly intermingled with connective tissue. We could not ascertain whether the connective tissue was replacing or

augmenting the glial fibrils. The gliosis merged gradually into the surrounding structures of the spinal cord. On the lateral surface of the upper lumbar portion of the spinal cord above the level of the intramedullary tumor there was a small flat hemangioblastoma, similar to that inside the lumbar portion of the cord. This small neoplasm was not noted on gross inspection of the spinal cord. It was attached to the pia mater and had produced a thickening of the pia-arachnoid. The blood spaces were similar to those in the tumor removed from the fourth ventricle; but there was very little swelling of the endothelial cells that lined the blood spaces, and xanthic cells were not present. The neoplasm in the right hemisphere of the cerebellum was an ependymoma of the cellular type.

The small tumor which we found in the right eye was a typical hemangioblastoma. There were many large thin-walled dilated blood spaces surrounded by

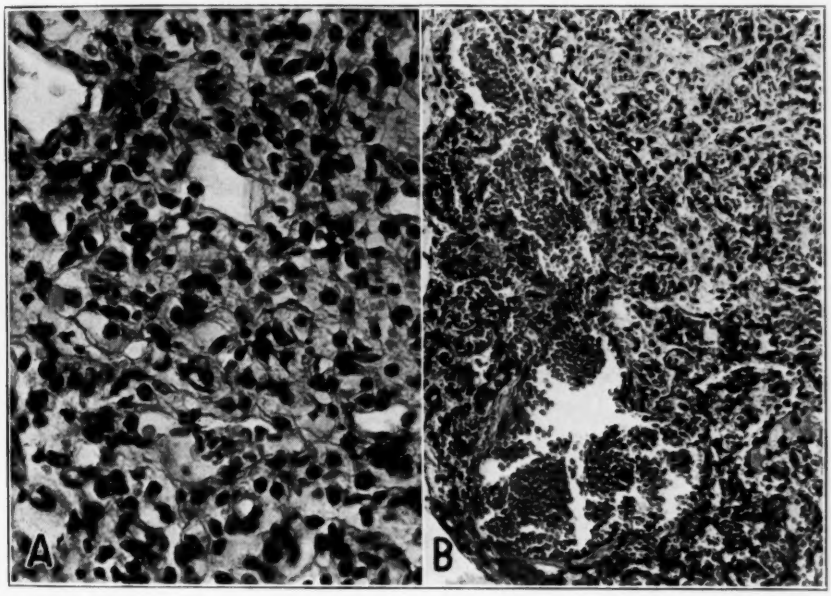


Fig. 8 (case 4).—*A*, photomicrograph of tumor in the left eye. Note the large number of extravascular cells. (Hematoxylin and eosin stain; × 325.) *B*, photomicrograph of hemangioblastoma from the right eye. Note dilated blood spaces filled with red blood cells and the paucity of extravascular cells. (Hematoxylin and eosin; × 160.)

numerous small capillaries. These blood spaces were open and were lined with flat endothelial cells, which were not swollen and were free of fat droplets. There were very few endothelial cells between the thin-walled capillary spaces (fig. 8 *B*). The tumor was near the posterior margin of the ciliary body but was within the retina, and there was no extension into either the ciliary body or the choroid. The tumor in the left eye was in the detached retina and was similar to that found in the retina of the right eye, except that many of the capillary blood spaces seemed to be obstructed by swollen endothelial cells that lined these spaces. Many swollen cells were present in the extravascular tissue between the blood spaces (fig. 8 *A*). The

cells were both intravascular and extravascular, were vacuolated and had a finely fenestrated appearance similar to that found in the tumor that was removed from the fourth ventricle. The detached retina was extensively degenerated, and in several small folds or pockets there were foreign body giant cells around clefts from which cholesterol crystals had been dissolved. There were no tumors in any other portion of this eye.

There were no hemangiomas in any other organs of the body. The cysts in the pancreas were dilated ducts unassociated with acinous tissue. We observed cysts in various stages of formation arising from the small ducts. The cysts in the kidneys were similar to those in the pancreas. In several there were small tumors; some of these were typical carcinomas (so-called hypernephroma) of the kidney, and others were so-called adenomas. Undoubtedly, these growths represented two stages of the same neoplastic process.

The adenoma of the left epididymis was a small growth made up of acini lined with low cuboidal epithelium. Histologic examination of Meckel's diverticulum showed no abnormalities.

## COMMENT

We have claimed, without complete justification, that all 4 of these patients presented the syndrome of Lindau–von Hippel disease. They all had angioma of the retina and hemangioblastoma of the cerebellum. The first 3 had a cyst associated with the angiomatous tumor, and the fourth patient had a small cyst at the upper pole of the neoplasm. The first 3 patients recovered after drainage of the cyst and resection of the mural nodule. We do not know whether there were any other stigmas of Lindau's disease because these 3 patients are living and well. There were no symptoms referable to syringomyelia or hemangioblastoma of the spinal cord. There were none referable to cysts of the pancreas, kidneys or any other organs or to adenomas or carcinomas of the kidneys.

Lindau observed that "the cystic pancreas is, in adults, almost pathognomonic for the syndrome." [2] We had no way of determining this in 3 of our cases, but we have classified them under the heading of Lindau–von Hippel disease because of the association of the retinal and cerebellar hemangioblastomas. It has never been established how many of the various malformations must be present before a case can justly be classified under the aforementioned heading. At necropsy it is easy to determine how many associated lesions exist, but in neurosurgical practice it is practically impossible to ascertain the presence of more than 2 lesions. We, therefore, feel justified in claiming that these 3 cases are examples of Lindau–von Hippel disease. The fourth case is a classic example of this disease, except that a cyst is not associated with the hemangioblastoma in the cerebellum. There have been a small number of cases of this disease in which there was a hemangioblastoma of the spinal cord and syringomyelia; not all, however, included the other criteria of Lindau–von Hippel disease.

It is generally agreed that almost all hemangioblastomas have endothelial cells both within and between the blood spaces, some of which are frequently laden with fat. The presence of such cells is so common that it is almost pathognomonic of hemangioblastoma. In case 4, we found two hemangioblastomas in which there were no lipoid-containing cells either within the blood spaces or between them. The small hemangioblastoma in the subarachnoid space and the tumor in the right eye contained no xanthic cells. The origin of the xanthic cells is not clear. Lindau [2] said of the fat: "This is apparently not a sign of degeneration but is to be ascribed to disturbances of circulation in the tumor tissue accompanied by stagnation of lymph rich in lipoids which is phagocytosed by the endothelial tumor cells, and this is transferred into foam cells." One wonders whether the swollen fat-laden endothelial cells are not an obstruction to the circulation of the blood, because of which there is a transudate which accumulates around the neoplasm and forms the cyst. In support of this hypothesis are the ocular findings in case 4 of our series. The small tumor in the right eye did not contain xanthic cells, and the retina was not detached. Both intervascular and intravascular endothelial cells of the angioma in the left eye were laden with fat, and in this eye there was a total detachment of the retina. Further observations will be necessary before we can be certain whether this hypothesis is right or wrong.

It is now generally accepted that Lindau's disease is the result of congenital malformations. It is interesting that in the 2 cases which we have studied completely (case 4 of our series and the one described by Kernohan, Woltman and Adson [10]) there was, in addition to those lesions associated with Lindau's disease, an ependymoma in the cerebellum. In neither case had the neoplasm produced symptoms, although in case 4 of this series the tumor measured 3 by 4 cm. Both were typical ependymomas belonging to the subtype designated cellular by Kernohan and Fletcher-Kernohan.[11] These 2 ependymomas were similar histologically to many other ependymomas we have observed, except that each was in a hemisphere of the cerebellum and not in contact with the ependyma of the fourth ventricle. Probably these 2 ependymomas are the result of malformations just as the hemangioblastomas, but it is impossible to distinguish them histologically from other ependymomas. We have no evidence at this time that all, or even any ependymomas

10. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord: A Review of Fifty-One Cases, with an Attempt at Histologic Classification, Arch. Neurol. & Psychiat. **25**:679-701 (April) 1931.

11. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of One Hundred and Nine Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:182-209, 1937.

are the result of malformation. These 2 cases are the only ones encountered in the literature in which there was an ependymoma of the cerebellum associated with Lindau's disease.

Clinically, all 4 cases were interesting. Case 1 presents an excellent example of an early manifestation of the retinal angioma which in its more chronic phase may be confused with other types of lesions of the retina; in this instance it simulated tuberculous choroidoretinitis with periphlebitis. Only with the development of cerebellar symptoms and intracranial hypertension was the retinal lesion suspected of being von Hippel's disease. The second and third cases, although differing in some respects, were more or less classic as regards the development and the diagnosis of the disease. The fourth case, again, presents a somewhat different clinical picture, which is explained by the observations at operation and necropsy. The surgical procedure employed in the 3 cases is more or less standardized, consisting in drainage of the cystic cavities, removal of the tumor nodule and removal of the wall of the cyst. The postoperative results were excellent, and the functional recovery was remarkable. In view of so many pathologic lesions in case 4 it is evident that any form of treatment was doomed to failure.

# INCIDENCE AND CAUSE OF DEATH IN SHOCK THERAPY

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The literature relative to the incidence and cause of death in shock therapy has been largely devoted to reports of individual cases. I have gathered as many of these as possible and have embodied the data in this analysis. In addition, material was obtained through nation-wide survey by means of a questionnaire, one page of which was related to insulin therapy and the other to metrazol therapy. The first item concerned the total number of patients treated. On the metrazol sheet the number of schizophrenic and the number of depressed patients treated were further particularized. The next inquiries concerned the number of deaths attributable either directly or indirectly to the treatment, the cause of death, whether or not an autopsy was performed and the autopsy report, if available. The last request was for a list of the complications other than those which resulted in death. This material will not be dealt with in this paper. Replies, with the data requested, were received from one hundred and forty-seven sources, including public institutions and clinics, veterans' facilities, private hospitals, clinics and sanatoriums and physicians in private practice. These reports came from thirty-six states and two Canadian provinces.

| | Insulin | Metrazol | Insulin and Metrazol |
|---|---|---|---|
| Number of cases..... | 12,234 | 18,543 | 291 |
| Number of deaths..... | 90 | 43 | 0 |
| Number of autopsies..... | 26 | 21 | 0 |

The total number of cases reported, the total number of deaths and the number of autopsies performed are tabulated. It will be noted that autopsies were performed in about 50 per cent of cases of death in the metrazol series and in somewhat over 25 per cent of cases of death in the insulin series. There may be some question regarding the diagnosis in the cases in which no autopsy was performed, and it must be admitted that replies were subjected to personal interpretation. However, every effort was made to limit the error from this source.

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Dr. Clifton T. Perkins, Commissioner of the Massachusetts State Department of Mental Health, compiled the statistics for Massachusetts, and Dr. N. L. Easton, of the Toronto Psychiatric Hospital, furnished similar material for the province of Ontario.

In table 1 all the deaths are analyzed according to cause. The first cause, hypoglycemic encephalopathy, includes those causes listed on the returns as protracted coma, irreversible coma, hypoglycemic shock and hyperinsulinism, and probably should include status epilepticus, which is listed separately. In cases in which these factors operated, autopsy, when performed, invariably revealed damage to the brain. Grossly, there were petechial hemorrhages and edema of varying degrees; microscopically, there were degenerative cell changes with congestion of small vessels. It is interesting to note the relatively low number of deaths due to cerebral causes with metrazol therapy. In the case reported as an instance of cerebral embolism the condition was secondary to an abdominal operation and pyonephrosis; it is thus

TABLE 1.—*Causes of Deaths During Insulin and Metrazol Therapy*

| | Insulin | Metrazol |
|---|---|---|
| Cerebral | | |
| Hypoglycemic encephalopathy | 38 | .. |
| Status epilepticus | 5 | .. |
| Hemorrhage and edema | 7 | 2 |
| Embolism | .. | 1 |
| Pulmonary | | |
| Aspiration pneumonia | 9 | 1 |
| Other pneumonias | 7 | 3 |
| Abscess of lung | 3 | 2 |
| Tuberculosis | 1 | 12 |
| Miscellaneous pulmonary | 2 | 3 |
| Cardiac | 12 | 9 |
| Miscellaneous | | |
| Acute nephritis | 1 | .. |
| Manic exhaustion | 2 | 2 |
| Peritonitis | .. | 2 |
| Intercurrent gastrointestinal infection | .. | 1 |
| Endarteritis obliterans | .. | 1 |
| Subacute bacterial endocarditis | .. | 1 |
| Acute myeloid leukemia | .. | 1 |
| Unknown | 3 | 2 |

excluded from those cases in which death was due directly to the treatment.

Aspiration pneumonia would be expected to be more frequent among patients undergoing insulin therapy, owing to the use of tube feeding in terminating the treatment. The report of 9 deaths among insulin-treated patients and 1 death among metrazol-treated patients confirms this assumption.

Under the heading of "other pneumonias," of the 7 cases in which pneumonia was associated with insulin therapy, 5 were of bronchopneumonia and 2 of pneumonia. Of the 3 cases in which pneumonia was attributable to metrazol therapy, pneumonia followed ether anesthesia for reduction of a fractured hip in 1 and occurred as a complication two months after fracture of the hip in another.

Arrested tuberculosis is, apparently, readily activated by metrazol treatment—12 deaths from tuberculosis being the largest number from

any single cause associated with this type of therapy. In the cases reported the disease was not active at the time treatment was started, and all the patients died within a year after treatments were stopped.

Under deaths from miscellaneous pulmonary conditions in the insulin series, the cause was given as empyema in 1 case and as pulmonary gangrene in the other, with the autopsy revealing subclinical bronchiectasis. The cause of the 3 deaths occurring in the metrazol series was reported as pulmonary infarction.

As cardiac causes coronary sclerosis and occlusion, myocarditis, cardiac collapse and acute dilatation were mentioned.

The miscellaneous causes were largely incidental to the treatment. The deaths due to manic exhaustion are exceptions. Peritonitis followed an appendical abscess in 1 case and was not related to treatment, while in the other it was due to rupture of the urinary bladder, resulting directly from the treatment.

TABLE 2.—*Relation of Causes of Death to Insulin and Metrazol Treatment* *

| Deaths | Insulin | Metrazol |
|---|---|---|
| Apparently not result of treatment | 1 (0.01%) | 6 (0.03%) |
| Not due directly to treatment | 36 (0.29%) | 31 (0.17%) |
| Resulting directly from treatment plus unknown factors | 53 (0.43%) | 6 (0.03%) |
| Total number of deaths | 90 (0.75%) | 43 (0.23%) |

* Figures in parentheses represent the death rate for this cause.

In table 2 the causes are considered from the point of view of their apparent relation to the treatment (table 2). The total number of deaths is given, with the mortality rate in parentheses. The one case in the insulin series in which death was probably unrelated to the therapy is that of acute nephritis. The 6 cases in the metrazol series in which death apparently was not the result of treatment include those of cerebral embolism, peritonitis from appendical abscess, intercurrent gastrointestinal infection, subacute bacterial endocarditis, acute myeloid leukemia and endarteritis obliterans. The second item, deaths "not due directly to treatment," arbitrarily includes deaths due to pulmonary and cardiac conditions, except in the case of aspiration pneumonia occurring during metrazol treatment, which is included under the direct causes. It was assumed that these causes were more or less indirect, for the reason that accessory procedures or preexisting contributory factors, such as tube feeding, reduction of fractures, arrested tuberculosis and cardiac damage, were involved. In the insulin series the direct causes include all of the cerebral conditions attributable to insulin; in the metrazol series the direct causes include cerebral conditions, in 2 cases; aspiration pneumonia, in 1 case, and peritonitis following rupture of the urinary bladder, in another. Also included in this figure

for both the insulin and the metrazol deaths were those due to "unknown causes," as it was felt that these were linked more or less directly with the treatment.

## CONCLUSIONS

The incidence of death is low with both forms of shock therapy: 73 per 10,000 patients treated with insulin and 23 per 10,000 patients treated with metrazol.

The death rate can be further reduced. Knowledge of the contributory factors, as brought out by this analysis, should be of aid. For instance, a closer check in the matter of tuberculosis might reduce by almost one third the death rate from this cause among metrazol-treated patients.

Reports in the literature indicate a definite increase in the rate of recovery for certain psychoses treated with insulin or metrazol, and I believe, in view of the low mortality rate, that the good results of shock therapy amply justify the risk taken.

# MULTIPLE PRIMARY TUMORS OF THE SPINAL CORD

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Multiple primary tumors of the spinal cord and its meninges are rare and, like those of the brain, are most frequently found accidentally at necropsy. In most instances the largest of the tumors produces the predominant symptoms, which mask those produced by the smaller new growths. In other cases the multiple growths may be asymptomatic, or the clinical picture may be that of a disseminated lesion of the spinal cord similar to that produced by multiple sclerosis or diffuse adhesive spinal arachnoiditis. In a study of 100 cases of glioma of the spinal cord by Foerster and Bailey [1] only 2 cases of multiple tumors were encountered, and in only 1 of Elsberg's [2] series of 81 cases of tumor of the spinal cord were multiple growths observed. Because of the infrequency of reports in the literature on multiple tumors of the spinal cord, a study of 2 cases and a discussion of their pathologic and clinical features seem justified.

## REPORT OF CASES

CASE 1.—*History.*—W. C., a white man aged 31 years, an automobile mechanic, entered the Michael Reese Hospital on Dec. 9, 1933. He stated that he had felt perfectly well until April of that year, when he noticed numbness and weakness of his left arm. One month later stiffness about the knee and ankle of his left leg appeared, and he had difficulty in raising his left foot off the floor. Difficulty in walking, with numbness particularly in the toes of his left foot, developed.

*Neurologic Examination.*—The essential neurologic findings on admission were restricted to the left side of the body, there being a Horner syndrome, slight weakness of the facial muscles, shoulder drop, weakness of the sternocleidomastoid muscle and slight atrophy of the first dorsal interosseous muscle, all on the left side. There was marked spasticity of both the upper and the lower extremity on the left side, and nystagmus on lateral gaze, with the quick component always to the side of fixation, was present.

*Diagnosis.*—The clinical impression was that of multiple sclerosis.

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From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine.

1. Foerster, O., and Bailey, P.: A Contribution to the Study of Gliomas of the Spinal Cord with Special Reference to Their Operability, in Thirty Years of the Scientific Activity of S. N. Davidenkov: General and Clinical Neuropathology, 1936, Leningrad, State Publishing Institute, 1936.

2. Elsberg, C. A.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, 1925, p. 325.

*Laboratory Data.*—Roentgen examination of the skull gave essentially negative results, the pineal gland being calcified and in normal position. On spinal puncture the Queckenstedt test revealed a block. T he spinal fluid was clear and had 2 lymphocytes per cubic millimeter, and the colloidal gold curve was 0011222000. Urinalysis gave normal results, and the Wassermann and Kahn reactions of the blood were negative.

*Course.*—On subsequent examinations sustained ankle clonus was obtained on the left side, the abdominal and cremasteric reflexes on that side were absent and there was some ataxia in the left leg. Because of the neurologic findings and the spinal block, the presence of a tumor in the high cervical portion of the spinal cord was strongly suspected. High cervical laminectomy, performed on Feb. 15, 1934, with removal of the second, third, fourth and fifth laminas, revealed that the dura mater was unchanged and the spinal cord was normal in size, shape and color. The wound was closed, and the patient left the hospital on March 21, with a final diagnosis of multiple sclerosis. He was readmitted to the Michael Reese Hospital on Aug. 19, 1935. He stated that he was able to work for a short time after leaving the hospital, but soon became very weak and was unable to continue. On reexamination there was no scanning speech but a small area insensitive to cotton in the left supraclavicular region and a zone hyposensitive to pinprick in the third thoracic region on the left side were noted. There was marked spasticity of all four extremities with lively tendon reflexes and bilateral Babinski and Hoffmann signs, and tremor of the right hand was noticed for the first time. The spinal block was still present, and roentgen examination of the spine revealed nothing abnormal. Because the spinal block had been present before operation and operation had revealed nothing pathologic, the diagnosis continued to be that of multiple sclerosis. The patient was discharged from the hospital on Nov. 7, 1935. On Feb. 21, 1937 he was admitted to the Cook County Hospital. He stated that there were times when the paralysis was not so severe but the remissions never lasted long. He now complained of pain in the right side of the face, and fibrillary twitchings in the platysma muscle on the right were seen. Urinary incontinence was noted a month before entrance.

On neurologic examination the patient was mentally alert, answered questions readily and was cooperative. There was marked spastic paralysis of all four extremities, with ankle clonus, lively reflexes and a bilateral Babinski sign. The right pupil was still larger than the left, and there was rapid nystagmus on lateral gaze. Examination revealed hypalgesia to pinprick below the shoulders and hypesthesia to cotton from the waist down. There were irregular patches of hypesthesia over the trunk, but position sense was present in the lower extremities. Spinal puncture revealed xanthochromic fluid, under a pressure of 12 mm. of mercury. The Pandy reaction was 3 plus, and the total protein was 91 mg. per hundred cubic centimeters. The Queckenstedt test revealed a block, and roentgen examination of the spine showed osteoarthritis. Because of the spinal block and the neurologic findings, a clinical diagnosis of adhesive spinal arachnoiditis was made. The patient did poorly; decubitus ulcers developed, and he died July 6, 1937, after an illness of approximately four years and three months.

*Necropsy.*—Through Dr. J. D. Kirshbaum, pathologist at Cook County Hospital, permission for postmortem examination of the brain and spinal cord was obtained. The anatomic diagnosis was multiple ependymomas of the spinal cord with extension of the cervical tumor into the medulla oblongata.

Macroscopic Observations: The brain was moderately swollen, and the leptomeninges were thin and transparent. The medulla oblongata and cervical portion

of the spinal cord, from the posterior border of the pons down to the second cervical spinal segment, were flattened, the greatest transverse diameter being 36 mm. On section of the brain, the cortex and basal ganglia were light gray-brown, the ventricles of medium width and the ependyma smooth. The inferior half of the pons showed light yellow-gray discoloration. In the medulla oblongata the discoloration became more marked, and below the olivary bodies, starting on the left side, was an irregular, grayish white, firm fascicular mass. In the upper cervical segments the entire transverse section was composed of grayish white, firm tissue, and it was only on the left side that a narrow zone of pale gray spinal cord substance remained. In the lower cervical segments the tumor was centrally soft and pale pink. Throughout the cervical, thoracic and lumbar segments of the spinal cord firm, fascicular, grayish white intramedullary tumors were observed.

Microscopic Observations: Blocks were taken at many levels of the spinal cord, embedded in paraffin and pyroxylin, and sections stained with toluidine blue, hemalum and eosin and Mallory's phosphotungstic acid hematoxylin and by the methods of Van Gieson and Weigert and Pal. Frozen sections were stained by the method of Perdrau and by Achucárro's fourth variant.

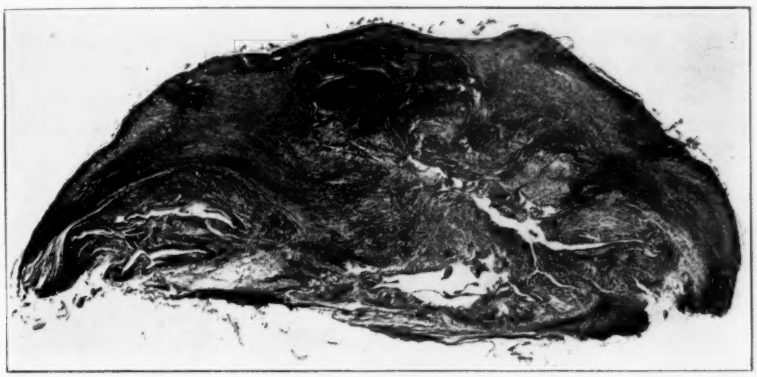

Fig. 1 (case 1).—Low power photomicrograph of a section through the cervical portion of the spinal cord, showing almost complete replacement of the substance of the spinal cord by a centrally cystic ependymoma. Mallory's phosphotungstic acid hematoxylin stain.

In the cervical portion (fig. 1) the spinal cord was greatly enlarged and, except for a narrow subpial zone of intact white substance, was completely replaced by a tumor, the central portion of which was cystic in places. This tumor extended from the upper levels of the medulla oblongata to the upper thoracic levels of the spinal cord. Throughout the thoracic and lumbosacral segments (fig. 2) were multiple, completely isolated, spherical and very cellular tumors. These tumors averaged 4 mm. in greatest diameter and were restricted to an anterior or to a lateral horn (fig. 2). At some levels there was proliferation of the ependymal tissue in the gray commissure. Sections through intervening levels of the spinal cord showed complete absence of tumor tissue, indicating that the new growths were distinct and separate.

The histologic structure of the isolated tumors throughout the thoracic and lumbosacral levels was, on the whole, rather uniform. In toluidine blue–stained sections its nosologic identity was easily discernible. Throughout the tumor were

a moderate number of thick-walled blood vessels surrounded by a clear, unstained area, and beyond this were groups of round to oval, vesicular nuclei, moderately rich in chromatin granules. In sections stained with Mallory's phosphotungstic acid hematoxylin the internuclear spaces were filled with a large number of fine, steel blue fibrils, which radiated to the adventitia of the blood vessels, entirely filling the clear perivascular spaces previously described in Nissl-stained sections.

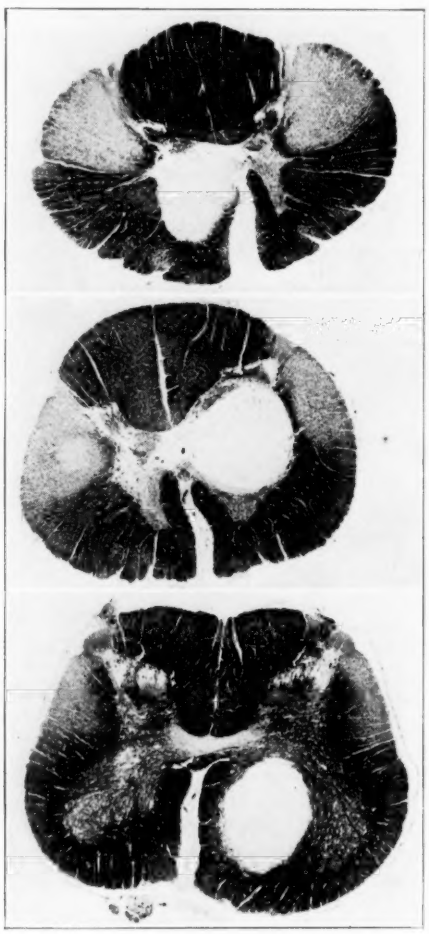

Fig. 2 (case 2).—Low power photomicrograph through several thoracolumbar levels of the spinal cord. The clear areas are the sites of ependymomas. Note the degeneration of the crossed pyramidal tracts. Myelin sheath stain.

No mitotic figures were seen. Study under an oil immersion lens revealed granules of blepharoplasten in the paranuclear spaces. These tumors were very cellular and compact, and the surrounding substance of the spinal cord showed few alterations, there being practically no zone of reactive gliosis. In sections stained by the method of Weigert and Pal degeneration of both crossed pyramidal tracts was marked (fig. 2). In the cervical portion (fig. 1) the histologic picture was,

on the whole, similar to that described at the thoracic and lumbosacral levels. The subpial zone was rich in fibrillar glia, and throughout the tumor were isolated ganglion cells derived from the gray columns which were completely enveloped by the tumor. These ganglion cells showed severe alterations, and the nerve fibers in their vicinity were fragmented. The central portion of the tumor at the cervical level was the site of an irregular cavity lined by fibrillar glia, and in this tissue were numerous thick-walled blood vessels. The perivascular spaces were rich in plasma cells, and throughout the loosened portion of the tumor the meshes between the glia fibrils were filled with histiocytes, laden with blood pigment.

Histologically, this case is one of multiple ependymomas of the spinal cord with extension of one of the growths into the medulla oblongata.

CASE 2.—*History.*—H. M., a white man aged 38, was admitted to the Research and Educational Hospitals on June 20, 1934 complaining of progressive atrophy of the muscles of the left forearm and of the right leg, of thirteen years' duration. He had noticed unsteadiness in gait for five years, and in the past one and one-half years deafness had developed. Visual disturbances of six months' duration were present, being more marked on the left. He stated that he had been well until thirteen years ago, when pain developed in the arches of his feet and he began to limp. He also noticed diminution in the size of his left arm and hand, the progress of which was rather slow until three years ago, when it became more rapid. About one and one-half years ago he noticed a roaring and whistling in his head. This roaring could not be localized and was soon followed by the development of deafness, first in the right ear and then in the left, until he became totally deaf. For the past five years progressive unsteadiness in his gait was noted, and about six months ago vision, first in his left eye and then in his right eye, became blurred. The family history was essentially irrelevant, and except for an attack of typhoid fever as a child and influenza two and one-half years ago, he had had no serious illness.

*Physical Examination.*—The patient did not appear acutely ill. Examination of the head and neck revealed essentially nothing abnormal. The lungs were clear, and the heart was not enlarged. The liver was palpated 2 fingerbreadths below the right costal margin. There was a bilateral pes cavus, and the calf of the right leg was smaller than the left. The left forearm and hand were smaller than the right, there being marked atrophy of the interosseous muscles and those of the thenar eminence.

*Neurologic Examination.*—The patient was well oriented, and the mental condition was good. His gait was ataxic, and he limped with his right leg. Visual acuity was diminished, the visual fields were contracted and the optic fundi were elevated 1 D. bilaterally. The pupils were round and regular and reacted both to light and on convergence. There was total deafness bilaterally. When tested for the Romberg sign he fell to the left. The superficial reflexes were easily elicited, but the patellar and achilles reflexes were absent; the other tendon reflexes were present. Vibration sense was impaired over the sacrum and in both legs.

*Diagnosis.*—The clinical impression was that of tumor of the brain, the residue of old poliomyelitis accounting for the muscular atrophy.

*Laboratory Examination.*—The results of urinalysis and determinations of the chemical constituents of the blood were within normal limits. The spinal fluid was clear, the Pandy reaction was 1 plus, the Queckenstedt test was positive and no cells were seen. The total protein of the spinal fluid measured 0.186 Gm.

per hundred cubic centimeters. The Wassermann reaction of the blood was negative, as was the Kahn reaction of the spinal fluid, but the Wassermann reaction of the spinal fluid with 1 and 2 cc. of fluid was 2 plus. The colloidial gold curve of the spinal fluid was of meningitic type. Flat roentgenograms of the skull were normal.

*Course.*—On June 30, 1934 ventriculographic examination revealed internal hydrocephalus. On the fifth postoperative day he had an attack of intense agitation and became disoriented. His temperature became elevated, and fibrillary twitchings were noted on the left side of the face. Later that day ventricular puncture was done, with the removal of 60 cc. of reddish fluid under markedly increased pressure. Breathing ceased but was resumed after two minutes of

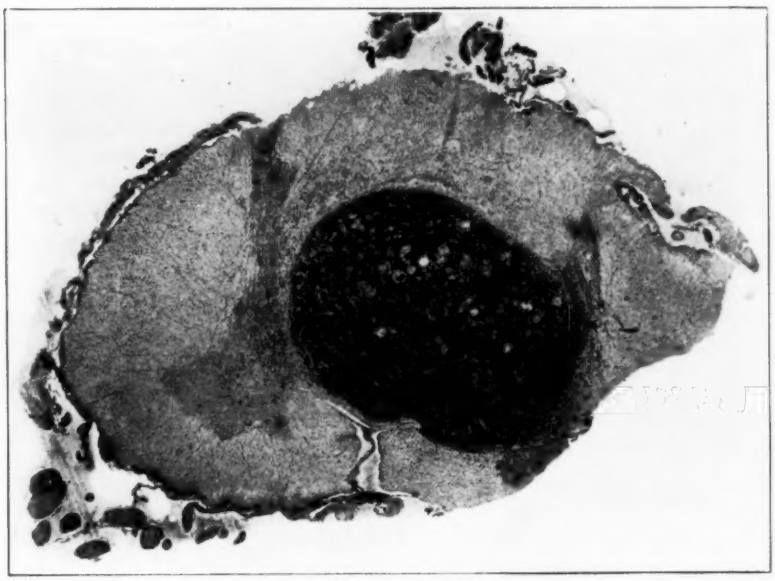

Fig. 3 (case 2).—Low power photomicrograph through a cervical section of the spinal cord, showing the intramedullary ependymoma. Toluidine blue stain.

artificial respiration and then became very deep. The ventricle was again tapped, but the patient did poorly and died on July 5.

*Necropsy.*—The anatomic diagnosis was neurinomas of both acoustic nerves; multiple neurinomas of the spinal nerve roots, especially those of the cauda equina; multiple intramedullary ependymomas of the spinal cord; dural meningioma in the thoracic region; focal and confluent bronchopneumonia of the lower lobe of the right lung; cloudy swelling of the myocardium, the liver and the kidneys; septic softening of the spleen.

Macroscopic Observations: Except for confluent areas of bronchopneumonia in the lower lobe of the right lung, the essential pathologic changes were in the central nervous system. In each cerebellopontile angle was a firm tumor, which on one side measured 5 by 3 cm. in greatest diameter and on the other 3 by 2 cm. The spinal cord was grossly normal. After being hardened in a 10 per cent concentration of solution of formaldehyde U. S. P., it was sectioned into segments

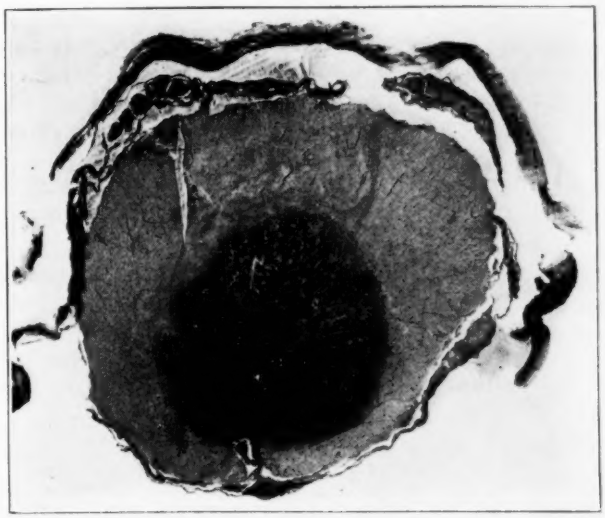

Fig. 4 (case 2).—Low power photomicrograph through an upper lumbar section of the spinal cord, showing the intramedullary ependymoma. Toluidine blue stain.

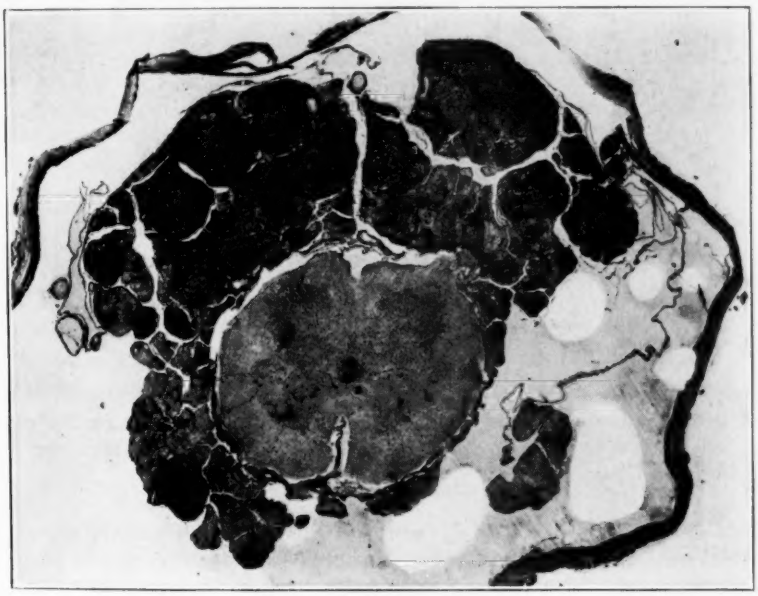

Fig. 5 (case 2).—Low power photomicrograph through the epiconus region of the spinal cord, showing the multiple neurinomas on the nerve roots in the cauda equina. Toluidine blue stain.

at every spinal nerve root. In the central portion of the spinal cord at the level of the cervical enlargement was a firm, spherical and fascicular, grayish white node. Throughout the thoracic levels were similar intramedullary grayish white nodules. In the upper thoracic segments a firm, grayish white tumor was attached to the inner aspect of the dura mater. Throughout the entire length of the spinal cord, especially in the cauda equina, definite spherical swellings in the spinal nerve roots were seen.

Microscopic Observations: Paraffin, pyroxylin and frozen sections from many levels of the spinal cord were studied microscopically with the same stains and

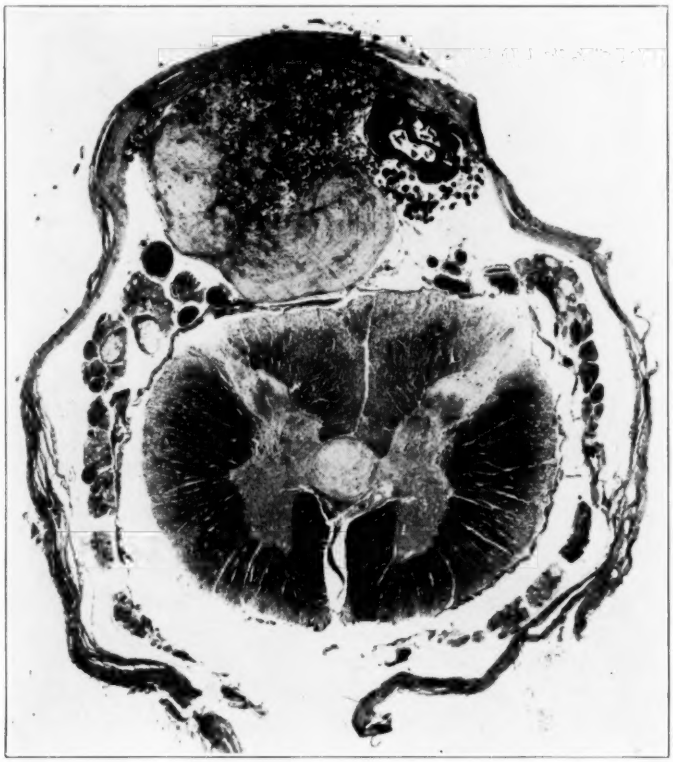

Fig. 6 (case 2).—Low power photomicrograph through a thoracic level of the spinal cord, showing the large meningioma, the small neurinomas on the nerve roots and marked central ependymal hyperplasia. Myelin sheath stain counterstained by Van Gieson's method.

methods as in the first case. As this work pertains to multiple primary tumors of the spinal cord, the changes in the brain in this remarkable case will be omitted. The intramedullary tumors varied considerably in size, the largest being in the cervical region (fig. 3). They were all of the same histologic character and were similar to the intramedullary growths described in case 1. Centrally, the one in the cervical region replaced the gray and white commissures and extended ventrally to the pia in the anterior median fissure, which was markedly shortened. Dorsally, it involved and compressed the ventralmost portions of the dorsal columns and extended laterally into the gray columns, more especially on the left side. Here it

involved the posterior and lateral horns and a large portion of the anterior horn. The motor ganglion cells in the intact most ventral portion of the left anterior gray column were few, distorted and surrounded by an increased number of gliocytes. In toluidine blue–stained sections the tumor was seen to consist morphologically of a moderate number of thick-walled blood vessels surrounded by a clear zone, which in sections stained with Mallory's phosphotungstic acid hematoxylin was filled with fine, steel blue fibrils, radiating to the adventitia of the blood vessels. Beyond this was a zone of vesicular chromatin-rich nuclei enveloped by bundles of glia fibrils. Mitotic figures were not seen, and in some places the lumens of the blood vessels were occluded by calcific masses. There was no zone of gliosis about the intramedullary tumors. In sections impregnated after the method of Perdrau fibers of reticulin were found only in relation to the blood vessels. Multiple granules of blepharoplasten were found in the paranuclear zone in frozen sections stained with Achucárro's fourth variant. In an upper lumbar segment (fig. 4) the tumor was centrally located. Many of the cervical, thoracic and lumbosacral spinal nerve roots were the site of spherical tumors, which in toluidine blue–stained sections were seen to be composed of interlacing fascicles of fibrillar tissue containing elongated, fusiform, chromatin-rich nuclei. This was most marked in the portion of the cauda equina about the conus and epiconus (fig. 5). In places the nuclei in these tumors were arranged in palisade formation. The growths on the spinal nerve roots were definitely neurinomatous in appearance and in Perdrau-impregnated sections were seen to contain innumerable reticulin fibrils. In the upper thoracic region of the spinal cord the inner aspect of the dura mater dorsal to the cord was the site of a tumor mass which measured up to 8 mm. in greatest diameter (fig. 6). This tumor was completely separated from the underlying arachnoid membrane, and it did not compress the spinal cord or its nerve roots. For the most part it was densely fibrotic, with only occasional elongated and compressed nuclei, and throughout were innumerable spherical calcareous concretions (psammoma bodies), which were laminated and which varied considerably in size. In some fields an island of bone was seen. The central ependymal tissue at this level was hyperplastic.

### PATHOLOGIC CONSIDERATIONS

From the histologic study of the cases presented it is evident that the multiple intramedullary tumors in both cases were ependymomas. Multiple neurinomas arising from the spinal nerve roots and a dural meningioma in the thoracic region were also present in the second case. Recklinghausen's disease is probably the most common disorder in which multiple tumors of the nervous system occur. In some cases the tumors are innumerable, arising from most of the nerve roots, especially those of the cauda equina. In rare instances neurinomas arise from within the substance of the spinal cord. Such a case was described by Walthard,[3] in which there were multiple neurinomas on the spinal nerve roots and a neurinoma in the cervical portion of the spinal cord.

3. Walthard, K. M.: Morbus Recklinghausen mit teilweiser intramedullären Localization und mit nervösbedingten Hyperthermie im postoperative Verlauf, Deutsche Ztschr. f. Nervenh. **99**:125, 1927.

In Reichmann's [4] case the intramedullary growth was in the thoracic segment. In such instances I believe that the intramedullary neurinoma arises from the nerves which accompany the intramedullary spinal arteries. In my second case large medullated nerve bundles were seen on the anterior spinal artery and on some of its intramedullary branches. In some places minute neurofibromas on these vessels were observed. More commonly, however, the intramedullary localization of the neurinoma results from invasion of the spinal cord by a growth arising from a nerve root. The association of meningiomas with neurofibromatosis, such as was observed in my second case, has been described by Katzenstein,[5] Beck,[6] Foerster and Gagel [7] and others. Intramedullary ependymomas, too, have been recorded in cases of neurofibromatosis by Kernohan and Parker,[8] Penfield and Young [9] and others. In some instances, as in my second case, the ependymomas, like the neurinomas, may be multiple. The probable functional relationship between the variety of pathologic conditions arising in multiple neurofibromatosis will be discussed in a more elaborate work subsequently. It should be remembered that there may be no external evidence of Recklinghausen's disease, such as café au lait patches in the skin or subcutaneous fibromas in such cases.

Next in frequency to the multiple tumors of the spinal cord associated with Recklinghausen's disease are the multiple intramedullary ependymomas, such as those in my first case. These tumors may vary considerably, from mild hyperplasia of the ependymal rests about the central canal to true neoplasia. As Cornil and Mosinger [10] emphasized, central medullary hyperplasia is frequent and may at times assume the proportions of a true benign tumor and be asymptomatic. They also

4. Reichmann, V.: Ueber einen operativ geheilten Fall von mehrfachen Rückenmarksgeschwülsten bei Recklinghausenschen Krankheit nebst Bemerkungen über das chemische und cytologische Verhalten des Liquor cerebrospinalis bei Gehirn- und Rückenmarksgeschwülsten, Deutsche Ztschr. f. Nervenh. **44**:95, 1912.

5. Katzenstein, R.: Ueber innere Recklinghausensche Krankheit, Virchows Arch. f. path. Anat. **286**:42, 1932.

6. Beck, E.: Zwei Fälle von Neurofibromatose mit Befallensein des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:748, 1939.

7. Foerster, O., and Gagel, O.: Ein Fall von Recklinghausenscher Krankheit mit fünf nebeneinander bestehenden verschiedenartigen Tumorbildungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:339, 1932.

8. Kernohan, J. W., and Parker, H. L.: A Case of Recklinghausen's Disease with Observations on the Associated Formation of Tumors, J. Nerv. & Ment. Dis. **76**:313, 1932.

9. Penfield, W., and Young, A. W.: The Nature of von Recklinghausen's Disease and the Tumors Associated with It, Arch. Neurol. & Psychiat. **23**:320 (Feb.) 1930.

10. Cornil, L., and Mosinger, M.: Sur les processus prolifératifs de l'épendyme médullaire, Rev. neurol. **1**:749, 1933.

stated that this hyperplasia is frequently metaplastic, and therefore it is logical to assume that the gliomas of the spinal cord can develop from ependymal tissue. This abnormal ependymal proliferation frequently occurs in the spinal dysraphic states resulting in myelodysplasia (Lichtenstein [11]). Kernohan and Kernohan [12] stated that shortly before puberty, and occasionally before that period, the central canal of the spinal cord becomes obliterated. During the process of obliteration the ependymal cells become disorganized and are distributed throughout the commissures as individual cells or small cell groups. Occasionally these cells form small secondary canals or rosettes. They expressed the belief that this disorganization of the ependymal tissue is a possible explanation of the large numbers of ependymomas occurring as primary tumors in the spinal cord. Multiple ependymomas of the spinal cord have been described by Gamper and Stiefler,[13] in whose case one growth was in the fifth and sixth cervical segments and another in the third and fourth lumbar segments. In the case of Marinesco and Goldstein [14] three intramedullary ependymomas were found: in the fifth cervical, the ninth thoracic and the third sacral segment, respectively.

Multiple hemangioblastomas of the spinal cord have also been observed. Lindau,[15] in describing the disease which now bears his name, presented 15 cases: Ten were from the literature and 5 were his own. In 4 of these 15 cases hemangioblastomas of the spinal cord were present, and in all of them the tumors were multiple (Wersilow,[16] Brandt,[17] Tannenberg [18] and Koch [19]). Since then multiple hemangio-

11. Lichtenstein, B. W.: "Spinal Dysraphism": Spina Bifida and Myelodysplasia, Arch. Neurol. & Psychiat. **44**:792 (Oct.) 1940.

12. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: Study of One Hundred and Nine Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**: 182, 1937.

13. Gamper, E., and Stiefler, G.: Ueber Rückenmarkstumoren mit dem klinische Bilde einer rasch tödlich verlaufenden spinalen Erkrankung, Deutsche Ztschr. f. Nervenh. **111**:239, 1929.

14. Marinesco, G., and Goldstein, M.: Contribution à l'étude des tumeurs associées du système nerveux, Ann. d'anat. path. **9**:457, 1932.

15. Lindau, A.: Studien über Kleinhirncysten. Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, supp. 1, p. 1.

16. Wersilow, W.: Zur Frage über die sogenannten serösen Zysten des Kleinhirns, Neurol. Zentralbl. **32**:350, 1913.

17. Brandt, R.: Zur Frage der Angiomatosis retinae, Arch. f. Ophth. **106**: 127, 1921.

18. Tannenberg, J.: Ueber die Pathogenese der Syringomyelie zugleich ein Beitrag zum Vorkommen der Capillarhämangiomen im Rückenmark, Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:119, 1924.

19. Koch, K.: Beiträge zur Pathologie der Bauchspeicheldrüse, Virchows Arch. f. path. Anat. **214**:180, 1913.

blastomas have been described by Wolf and Wilens [20] and by Guillain, Bertrand and Lereboullet.[21] Multiple meningiomas have also been described; in the case of Marinesco and Goldstein [14] they were associated with multiple intramedullary ependymomas.

To a miscellaneous group may be added the multiple spinal lipomas, which are, as a rule, extradural (Hoffmann [22]), the multiple spinal osteomas (Zanda [23]) and the multiple dermoid cysts of the spinal cord and meninges (Trachtenberg [24]).

Metastatic lesions of the spinal cord and carcinomatosis, sarcomatosis and gliomatosis of the leptomeninges do not belong to this group of primary multiple tumors of the spinal cord, nor do the epidural masses: the lymphoblastoma and the granuloma. Secondary involvement of the spinal cord by growths in the vertebral bodies (carcinoma, myeloma, etc.) are common but, like the group just mentioned, do not properly belong to this discussion.

## CLINICAL CONSIDERATIONS

The clinical diagnosis of an intramedullary tumor of the spinal cord may be extremely difficult to make, and that of multiple tumors may be even more so. Foerster and Bailey [1] stated that it is generally agreed that Nonne was right when he insisted that there is no pathognomonic sign of intramedullary tumor. The ependymomas constitute the largest group of intramedullary tumors, and as a rule they grow slowly. In my first case the clinical course was of five years' duration, and in the second it was of over thirteen years' duration. Many times the growths are infiltrative, enveloping ganglion cells and nerve fibers, which continue to function. Because of this, there may be a seeming disparity between the size and localization of the new growth and the clinical symptoms, such as are associated, for example, with the pontile gliomas. In my first case the diagnosis of a tumor of the spinal cord involving the cervical region was made relatively early in the evolution of the growth. As so frequently happens, however, failure to find the tumor in the first exploration precluded subsequent attempts. The symptoms produced by the large cervical tumor did much to mask those resulting from the smaller thoracolumbar growths. The clinical picture toward the termina-

20. Wolf, A., and Wilens, S. L.: Multiple Haemangioblastomas of the Spinal Cord with Syringomyelia, Am. J. Path. **10**:545, 1934.

21. Guillain, G.; Bertrand, I., and Lereboullet: Hémangioblastome du système nerveux central à localisations multiples, Rev. neurol. **1**:432, 1932.

22. Hoffmann, K., cited by Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 480.

23. Zanda, L.: Ueber die Entwicklung der Osteome der Arachnoidea spinalis, Beitr. z. path. Anat. u. z. allg. Path. **5**:391, 1889.

24. Trachtenberg, M. A.: Ein Beitrag zur Lehre von den arachnoidealen Epidermoiden und Dermoiden des Hirns und Rückenmarks, Virchows Arch. f. path. Anat. **154**:274, 1898.

tion of the illness was that of a disseminated lesion and multiple sclerosis was strongly considered, but because of the spinal fluid findings a diagnosis of adhesive arachnoiditis was decided on. It is interesting to note that urinary incontinence did not appear until six months before the patient's death. In my second case the ependymoma involving the substance of the cervical enlargement on the left side expressed itself clinically in the form of progressive atrophy of the muscles of the left forearm and hand, and one of the growths in the lumbar enlargement had produced atrophy of the muscles of the right leg. Since fibrillation and sensory disturbances were lacking and since the muscular atrophy was flaccid, degenerative and atrophic, the diagnosis of an old poliomyelitis was made to account for the muscular atrophy. The symptom complex produced by tumors of the cerebellopontile angle did much to subordinate the attention given to the other neurologic findings. It is interesting to note that flaccid, degenerative and atrophic muscular atrophy involving groups of muscles irregularly without sensory disturbances or fibrillary twitchings often leads to the diagnosis of an old poliomyelitis because of the almost characteristic appearance of the extremities, and the patient's story of the progressive character of the disorder is often overlooked. In a case of intramedullary ganglioneuroma of the spinal cord described by Lichtenstein and Zeitlin,[25] muscular atrophy of seventeen years' duration resulting in severe kyphoscoliosis was also considered clinically to be due to an old poliomyelitis. It may be well to emphasize that a protracted clinical course, of even fifteen years or more, does not preclude the presence of an intramedullary tumor. A striking feature in my second case was the presence of multiple neurofibromas on the nerve roots which were asymptomatic. Such a condition has been noted repeatedly, and the growths are often discovered accidentally at necropsy. The dural meningioma in the thoracic region, too, was asymptomatic despite its large size, for it did not infringe on the nerve roots or compress the spinal cord. It is well to remember that cutaneous manifestations may be absent in generalized neurinomatosis of the spinal nerve roots.

SUMMARY

The clinical and pathologic features of 2 cases of multiple intramedullary tumors of the spinal cord are presented. Multiple intramedullary tumors are most frequently ependymomas, and they may be associated with Recklinghausen's disease of the central nervous system. The association of ependymomas with neurinomas and meningiomas is emphasized. The clinical course of such tumors may be greatly protracted, and frequently many of the growths are asymptomatic.

25. Lichtenstein, B. W., and Zeitlin, H.: Ganglioglioneuroma of the Spinal Cord Associated with Pseudosyringomyelia, Arch. Neurol. & Psychiat. **37**:1356 (June) 1937.

# CEREBROSPINAL FLUID DYNAMICS IN MAN

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CINCINNATI

Although Quincke [1] introduced the technic of lumbar puncture in 1891, it was not until 1916 that Queckenstedt [2] stressed the importance of cerebrospinal fluid dynamics. Queckenstedt pointed out that in the presence of obstructive lesions of the subarachnoid space the rise in cerebrospinal fluid pressure which normally follows compression of the veins of the neck (mainly the internal jugulars) does not take place. A further step in the interpretation of the abnormal dynamic responses of the cerebrospinal fluid which occur with blockage of the spinal subarachnoid space was made by Ayer [3] in 1921, when he introduced the technic of combined cisternal and lumbar puncture.

Attempts have been made to quantitate the dynamics of the cerebrospinal fluid. Stookey, Merwarth and Frantz [4] and Stookey and Klenke [5] described a modification of the Queckenstedt test. They suggested that the response of the cerebrospinal fluid pressure following manual bilateral jugular compression should be divided into three phases, which they charted as follows: (1) response to instantaneous "touch com-

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1. Quincke, H.: Die Lumbalpunction des Hydrocephalus, Berl. klin. Wchnschr. **28**:929-965, 1891.

2. Queckenstedt: Zur Diagnose der Rückenmarkskompression, Deutsche Ztschr. f. Nervenh. **55**:325-333, 1916.

3. Ayer, J. B.: Spinal Subarachnoid Block as Determined by Combined Cistern and Lumbar Puncture, with Special Reference to the Early Diagnosis of Cord Tumor, Tr. Am. Neurol. A. **47**:272, 1921; Arch. Neurol. & Psychiat. **7**:38-52 (Jan.) 1922.

4. Stookey, B.; Merwarth, H. R., and Frantz, A. M.: A Manometric Study of the Cerebrospinal Fluid in Suspected Spinal Cord Tumors, Surg., Gynec. & Obst. **41**:429-442, 1925.

5. Stookey, B., and Klenke, D.: A Study of the Spinal Fluid Pressure in the Differential Diagnosis of Disease of the Spinal Cord, Arch. Neurol. & Psychiat. **20**:84-109 (July) 1928.

pression," (2) rise and fall on deep compression and release and (3) change in the pressure level after withdrawal of 7 cc. of fluid ("pressure index"). Stookey and his associates regarded a rise in cerebrospinal fluid pressure to 300 to 500 mm. of water as the normal response to ten seconds of manual jugular compression. Grant and Cone [6] suggested the use of a quantitative method for measuring the effect of jugular compression on the pressure of the cerebrospinal fluid. They applied a blood pressure cuff to the neck and raised the pressure in the cuff to 20, 40, 60, 80 and 100 mm. of mercury at intervals. The level of the cerebrospinal fluid pressure was charted at the end of ten seconds of compression at each of these pressures. After deflation of the cuff, the fall in the cerebrospinal fluid pressure was recorded by noting the pressure at ten second intervals until it returned to its original level.

During the development of a method for measuring intracranial blood flow, a number of factors have been encountered which influence the response of the cerebrospinal fluid pressure to jugular compression. Because of their importance in the clinical evaluation of cerebrospinal fluid dynamics, they are presented in this paper.

## METHOD

The patient was placed in the lateral recumbent position and the head supported in a position so that its center was on the same level as the vertebral column. Lumbar puncture was performed usually between the third and the fourth lumbar vertebra, using an 18 gage Fremont-Smith needle. Pressures were measured with an Ayer water manometer, graduated to 700 mm. with the lumbar portion of the spine as a reference point. A latex rubber cuff, to be described subsequently, was snugly applied to the neck, and the initial cerebrospinal fluid pressure was recorded after ascertaining that the patient was relaxed, that the deflated cuff did not influence the pressure and that the pressure level was stable. The neck cuff was then inflated by the routine application of a pressure of 40 mm. of mercury (544 mm. of water), and the level of the maximum response of the cerebrospinal fluid pressure was recorded. The cuff was then deflated and the final cerebrospinal fluid pressure recorded. A cuff pressure of 40 mm. of mercury was chosen because higher pressures caused considerable discomfort to the patient, sometimes resulting in hyperpnea and straining. The response of the cerebrospinal fluid pressure to manual bilateral jugular compression was also tested in each case in order to compare it with the response obtained with the cuff. Many of these observations were made in conjunction with studies of the blood flow, the technic of which is described elsewhere.[7] In some of the latter experiments, the cerebrospinal fluid pressure was initially adjusted to from 180 to 200 mm. of

6. Grant, W. T., and Cone, W. V.: Graduated Jugular Compression in the Lumbar Manometric Test for Spinal Subarachnoid Block, Arch. Neurol. & Psychiat. **32**:1194-1201 (Dec.) 1934.

7. Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, with Observations on Hydrodynamics of the Craniovertebral System, Arch. Neurol. & Psychiat., to be published.

water by injecting Ringer's solution into the subarachnoid space. Because of this procedure, the average initial cerebrospinal fluid pressures with which we worked in this series were higher than the usual normal initial pressure. The reason for elevating the pressure is stated elsewhere; however, it has been determined that such an elevation of the initial cerebrospinal fluid pressure does not affect significantly the maximum level of the pressure during jugular compression except when the initial pressure is abnormally low.

In those cases in which the intracranial blood flow was estimated, the rate of volume displacement of cerebrospinal fluid through a large needle was determined during maximum compression of the veins of the neck (at cuff pressures of 60 to 80 mm. of mercury). In the latter procedure the cerebrospinal fluid pressure remained constant during the displacement.[7] Therefore information concerning the response of the cerebrospinal fluid to jugular compression was obtained under two conditions: (1) The magnitude of change in cerebrospinal fluid pressure was determined at a constant cerebrospinal fluid volume, and (2) the rate of change in cerebrospinal fluid volume was determined at a constant cerebrospinal fluid pressure.

## RESULTS

*Influence of Various Types of Occlusion Cuffs.*—On comparing the response of the cerebrospinal fluid pressure to inflation of a neck cuff with that obtained by manual jugular compression, it became obvious that ordinary blood pressure cuffs did not effectively compress the neck veins. The degree of their effectiveness varied with the size and shape of the neck and also with the manner of application. A cuff system was, therefore, devised by one of us (E. B. F.) which appeared to overcome this difficulty. A flat, hollow latex rubber cuff,[8] 36 cm. long and 7 cm. wide, was constructed so that the inner side (to be placed next to the neck) not only was much thinner but had a total area greater than the area of the outer side. The inner layer, because of its excess area, had the capacity to expand freely for a distance of 2.5 cm. Because of its thinness, volume changes in the cuff which exceeded its "free" capacity required little excess pressure. The outer side was made rigid by embedding in it a continuous layer of nondistensible cloth. The rubber cuff was placed around the neck, with the thin surface inward, and held securely in place by buckling around the cuff an inelastic canvas belt of the same width. When pressure was applied to this cuff, expansion in an outward direction was limited by the thick outer wall of the cuff and the surrounding inelastic canvas belt, while the inner side, being freely distensible, could change in volume and at the same time transmit all of the pressure within the cuff to the underlying structures. A comparison of the cerebrospinal fluid dynamic responses obtained by using this cuff with those obtained with the use of other types of cuffs (table 1) indicates that it is much more effective in compressing the neck veins.

8. The cuff was made by Waldo Yonker, department of biochemistry, University of Cincinnati College of Medicine.

This cuff has been used to compress the neck veins in the studies on 124 cases to be reported. The response of the cerebrospinal fluid pressure to a pressure of 40 mm. of mercury in this cuff has been compared with the response to firm manual bilateral jugular compression in all cases. In the 60 cases in which the cerebrospinal fluid pressure approached that in the cuff, bilateral jugular compression likewise caused a prompt and marked rise of the cerebrospinal fluid pressure.[9] In only 6 of 64 cases in which the response of cerebrospinal fluid pressure to cuff pressure was definitely diminished[10] did manual compression produce a significantly better response. Therefore, with the possible exception of these 6 cases, it is evident that the cuff effectively compressed the neck veins.

These results demonstrate that the usual types of compression cuffs will not quantitatively compress the deep veins of the neck, but that the cuff described here probably does (table 1).

TABLE 1.—*Cerebrospinal Fluid Pressures During the Application of Pressures of 20, 30 and 40 Mm. of Mercury to Different Types of Neck Cuffs in a Single Patient*

| | | | |
|---|---|---|---|
| Pressure applied to neck cuff: | | | |
| Mm. mercury | 20 | 30 | 40 |
| Mm. water | 270 | 410 | 544 |
| Response of cerebrospinal fluid pressure, mm. cerebrospinal fluid | | | |
| Narrow cuff | 210 | 250 | 250 |
| Regular blood pressure cuff | 275 | 350 | 405 |
| Ferris cuff | 315 | 435 | 500 |

*Effect of Leakage of Cerebrospinal Fluid.*—In 17 cases in which initial cerebrospinal fluid pressures ranged from 110 to 200 mm. of water (average 182 mm. of water), the response to a cuff pressure of 40 mm. of mercury (544 mm. of water) averaged 398 mm. of water (with a range from 290 to 470 mm.). In these cases the response to manual jugular compression was likewise poor. On analysis of these results it was found that the poor response to cuff pressure could be explained on the basis of leakage of cerebrospinal fluid from the site of puncture. Leakage was demonstrated by the fact that the cerebrospinal fluid pressure returned to a level lower than the original one after the trial of "pressure dynamics." The fall in pressure below the initial level was, in all cases, 30 mm. of water or more. When the pressure of the cerebrospinal fluid was adjusted to its former initial level by the introduction of Ringer's solution into the subarachnoid space and the cuff pressure

9. Generally, the pressure exceeded the height of the manometer.

10. Responses of cerebrospinal fluid pressure (to 40 mm. of mercury of occlusion pressure) below 480 mm of water were considered to be diminished.

was applied and released, there was, again, a similar fall of the cerebrospinal fluid pressure below its initial level. Such leakage was most often observed in subjects in whom lumbar puncture had been performed one to two days prior to these studies, and, occasionally, it resulted from undue trauma in the process of lumbar puncture. It may be concluded that leakage of cerebrospinal fluid can be detected if it occurs and that such leakage definitely depresses the response of the cerebrospinal fluid pressure to jugular compression.

*Effect of Low Initial Cerebrospinal Fluid Pressure.*—One of the most interesting phenomena observed was the depressing effect of a low initial cerebrospinal fluid pressure on the dynamic pressure response. In 10 cases in which there was an average initial cerebrospinal pressure

TABLE 2.—*Effect of Elevation of Low Initial Cerebrospinal Fluid Pressure on Response of Cerebrospinal Fluid Pressure to 40 Mm. of Mercury (544 Mm. of Water) Cuff Pressure*

| Case No. | Initial Cerebrospinal Fluid Pressure, Mm. $H_2O$ | Response to 544 Mm. $H_2O$ Cuff Pressure, Mm. $H_2O$ | Adjusted Cerebrospinal Fluid Pressure, Mm. $H_2O$ * | Response to 544 Mm. $H_2O$ Cuff Pressure, Mm. $H_2O$ |
|---|---|---|---|---|
| 1 | 50 | 185 | 150 | 430 |
| 2 | 110 | 330 | 220 | 520 |
| 3 | 50 | 150 | 180 | 470 |
| 4 | 95 | 250 | 185 | 500 |
| 5 | 140 | 350 | 180 | 460 |
| 6 | 120 | 260 | 220 | 535 |
| 7 | 90 | 250 | 205 | 550 |
| 8 | 100 | 290 | 210 | 430 |
| 9 | 110 | 210 | 210 | 430 |
| 10 | 90 | 210 | 190 | 410 |
| Average | 96 | 249 | 195 | 474 |

* The initial pressure was elevated by the introduction of sterile Ringer's solution into the subarachnoid space.

of 96 mm. of water, the maximum level of cerebrospinal fluid pressure on application of a cuff pressure of 40 mm. of mercury (544 mm. of water) averaged only 249 mm. of water (table 2). After the elevation of the initial cerebrospinal fluid pressure to an average value of 195 mm. of water by injecting Ringer's solution into the subarachnoid space, the average response was 474 mm. of water.

As a corollary to this set of experiments, the initial pressure was lowered from an average of 202 mm. of water to one of 113 mm. in 6 cases. The response of the cerebrospinal fluid pressure to a pressure of 40 mm. of mercury on the neck, which had averaged 523 mm. of water initially, fell to 308 mm. of water as the result of lowering the initial pressure (table 3).

Low initial pressures were most often encountered in patients in whom lumbar puncture had been performed recently and considerable

fluid removed. Several examples were noted in patients who were dehydrated. Regardless of the cause of the low pressure, it is evident that it may be responsible for poor responses of cerebrospinal fluid pressure to jugular compression. The cause of this phenomenon appears to be related to the presence of initially distended intracranial veins in persons with low intracranial pressure.[7]

TABLE 3.—*Effect of Depression of Initial Cerebrospinal Fluid Pressure on Response of Cerebrospinal Fluid Pressure to 40 Mm. of Mercury (544 Mm. of Water) Cuff Pressure*

| Case No. | Initial Cerebrospinal Fluid Pressure, Mm. $H_2O$ | Response to 544 Mm. $H_2O$ Cuff Pressure, Mm. $H_2O$ | Adjusted Cerebrospinal Fluid Pressure, Mm. $H_2O$ * | Response to 544 Mm. $H_2O$ Cuff Pressure Mm. $H_2O$ |
|---|---|---|---|---|
| 1 | 190 | 540 | 120 | 350 |
| 2 | 180 | 520 | 90 | 370 |
| 3 | 210 | 515 | 130 | 275 |
| 4 | 220 | 525 | 120 | 260 |
| 5 | 215 | 505 | 130 | 340 |
| 6 | 195 | 530 | 90 | 250 |
| Average | 202 | 523 | 113 | 308 |

* The initial pressure was decreased by the removal of cerebrospinal fluid.

TABLE 4.—*Relation of Height of Cerebrospinal Fluid Pressure Response (with Occlusive Pressure of 40 Mm. of Mercury) to Rate of Cerebrospinal Fluid Displacement During Maximum Jugular Compression*

| | Average Rate of Cerebrospinal Fluid Displacement, Cc. per Min. | Response of Cerebrospinal Fluid Pressure to 40 Mm. Hg Cuff Pressure, Mm. $H_2O$ |
|---|---|---|
| Ineffective cuff | 98 | 405 |
| Effective cuff (same case) | 113 | 500 |
| Low initial pressure (50 mm.) | 36 | 185 |
| Pressure raised to 200 mm. $H_2O$ (same case) | 75 | 510 |
| Hyperventilation | 62 | 275 |
| Normal breathing (same case) | 80 | 460 |
| Nicotinic acid, 20 mg. intravenously | 144 | 410 |
| Control (same case) | 117 | 330 |
| Pressure dynamic responses below 480 mm. (17 cases) | 97 (weighted average) | 365 (average) |
| Pressure dynamic responses above 480 mm. (36 cases) | 121 (weighted average) | 517 (average) |

*Effect of Hyperventilation.*—In 6 instances in which hyperpnea was present during the study, the dynamic responses were inadequate.

Control patients were, therefore, asked to hyperventilate, and during this period it was demonstrated that the response of the cerebrospinal fluid pressure to jugular compression during voluntary hyperventilation was significantly less than during normal breathing (table 4). It can be concluded that the poor pressure responses in the 6 subjects who were hyperpneic during the test were due, in part at least, to hyperventilation.

*Effect of Spinal Subarchnoid Block.*—The dynamic responses obtained from combined cisternal and lumbar puncture in 2 such cases are presented in table 5. The block was caused by adhesive spinal arachnoiditis in both instances.

*Other Factors Affecting the Cerebrospinal Fluid Dynamic Responses.*—So far, an adequate reason for the occurrence of poor dynamic responses has been advanced in 41 cases. Of the remaining 83 cases, the application of a pressure of 40 mm. of mercury (54 cm. of water) to the neck cuff caused an elevation in the cerebrospinal fluid pressure to 480 mm. of water or above in 60 persons (72 per cent) and to below 480 mm. in 23 persons (28 per cent). The level of 480 mm. of water was arbitrarily selected as a value for separating the groups into those with "adequate" and those with "inadequate" dynamic responses, because values above this figure were never obtained in the presence of low

TABLE 5.—*Comparison of Simultaneous Lumbar and Cisternal Cerebrospinal Fluid Pressure Dynamic Responses in Two Cases of Spinal Subarachnoid Block*

| | | Cerebrospinal Fluid Pressure, Mm. $H_2O$ | | |
|---|---|---|---|---|
| | Site of Puncture | Initial Pressure | Response to 40 Mm. Hg Cuff Pressure | Final Pressure |
| Patient A. W. | Lumbar region | 130 | 190; slow | 110 |
| | Cistern | 140 | 410; prompt | 140 |
| Patient S. H. | Lumbar region | 180 | 240; slow | 160 |
| | Cistern | 175 | 510; prompt | 165 |

initial pressures or of leakage of the cerebrospinal fluid. It is believed that the difference between this cerebrospinal fluid pressure (480 mm. of water) and the pressure applied to the neck (544 mm. of water) is well within the limits of error of the method.

The cause of the inadequate pressure responses in this group of 23 patients is difficult to determine. Since the response of cerebrospinal fluid pressure to manual jugular compression was likewise inadequate,[11] it is clearly not related to ineffectiveness of the cuff in compressing the deep veins of the neck.

Gibbs, Gibbs and Lennox[12] have shown that hyperventilation depresses the cerebral blood flow. Therefore the fact that hyperven-

11. In these patients cerebrospinal fluid pressure above 500 mm. of water were rarely obtained by means of manual jugular compression, whereas in the group having adequate dynamic responses the pressure readily rose to 600 mm. and above.

12. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Physiol. **111**:557-563, 1935.

tilation depresses the dynamic pressure (table 4) indicates that poor dynamic responses may be caused by an abnormally slow cerebral blood flow. Furthermore, the intravenous administration of nicotinic acid, which increases the intracranial blood flow,[13] has been demonstrated to enhance the response of the cerebrospinal fluid pressure to jugular compression (table 4). Although the exact cause cannot be determined with the evidence at hand, it may be that the poor dynamic responses in this group of patients are accounted for by the presence of a relative diminution in intracranial blood flow.

*Relation of the Rate of Change in Cerebrospinal Fluid Volume to the Level of Cerebrospinal Fluid Pressure During Jugular Compression.*—In the interpretation of cerebrospinal fluid dynamics, the rate at which the cerebrospinal fluid pressure rises during jugular compression has been considered to be as important as is the final height to which it rises. Wtih the use of a manometer which has a very short period of lag, it has been shown that during jugular compression the cerebrospinal fluid pressure rises almost instantaneously.[7] The much slower rise in pressure noted in the ordinary water manometer is the result of a lag in the method of recording. This rise really represents the rate at which the cerebrospinal fluid volume changes from the initial level of fluid in the manometer to the level reached when the pressure in the manometer finally becomes equal to that within the subarachnoid space. In our experiments, qualitative estimates indicated that in general the lower the height to which the cerebrospinal fluid pressure rose the slower the rise of the fluid level in the manometer.

The quantitative measurement of rates of displacement of the cerebrospinal fluid obtained with the use of a large needle in the subarachnoid space during a period when the cerebrospinal fluid pressure remained constant [7] obviously offered a much more accurate index of the rate of change in cerebrospinal fluid volume during jugular compression than that obtained by means of the usual small bore lumbar puncture needle. The rate of displacement of cerebrospinal fluid was recorded in a number of patients in each of the groups previously described, and a summary of this information is presented in table 4. These results indicate that there is a correlation between the rate of change in cerebrospinal fluid volume and the level to which the cerebrospinal fluid pressure rises during jugular compression. They also demonstrate that the same factors must be considered in the interpretation of rate of rise of cerebrospinal fluid pressure as in the interpretation of the final height to which the pressure rises.

13. Aring, C. A.; Ryder, H. W.; Roseman, E.; Rosenbaum, M., and Ferris, E. B., Jr.: The Effect of Nicotinic Acid and Related Substances on the Intracranial Blood Flow of Man, Arch. Neurol. & Psychiat., to be published.

## COMMENT

In order to use the response of the cerebrospinal fluid pressure to jugular compression as an indication of subarachnoid spinal block, it is essential that the lower limit of pressure response in subjects without block should not exceed the upper limit in patients with varying degrees of block. It is apparent that comparative values for the cerebrospinal fluid pressure cannot be obtained by manual jugular compression, because of the human element, or by the use of the ordinary blood pressure cuffs, because of their variable effectiveness. Even though we have controlled this variable factor by using a cuff which appears to compress effectively the deep veins of the neck, extremely poor responses of cerebrospinal fluid pressure to jugular compression have been obtained in many persons who did not have spinal subarachnoid block.

Although in the majority of subjects it has been possible to demonstrate a technical or physiologic reason for the poor response of cerebrospinal fluid pressure, nevertheless, for clinical purposes, the method of measuring the response of lumbar cerebrospinal fluid pressure to jugular compression will not serve for an accurate diagnosis of the presence or absence of pathologic block. However, if one keeps in mind the factors which cause variation in cerebrospinal fluid responses, the method should prove of value in ruling out block in many cases in which poor dynamic responses occur. In this manner, the number of cases in which partial or total subarachnoid block is suspected will be limited accordingly and further diagnostic procedures curtailed. In the final analysis, comparison of simultaneous dynamic responses of the cerebrospinal fluid pressure in the lumbar and in the cisternal subarachnoid spaces, as recommended by Ayer, appears to be the only accurate hydrodynamic method for diagnosing spinal subarachnoid block.

## SUMMARY

A new type of neck cuff which appears to compress effectively the deep veins of the neck is described.

The response of the cerebrospinal fluid pressure to jugular compression, either in terms of magnitude or of rate of rise, may be greatly influenced by (1) the manner in which the neck veins are compressed, (2) the initial cerebrospinal fluid pressure, (3) leakage of cerebrospinal fluid, (4) hyperventilation, (5) variations in intracranial blood flow and (6) pathologic block in the spinal subarachnoid space.

A knowledge of these variable factors should aid in the clinical interpretation of dynamic responses of the cerebrospinal fluid pressure.

Nathaniel Brower, Ph.D., and Jane K. Friedlander gave technical assistance.

# PREVENTION OF TRAUMATIC COMPLICATIONS IN CONVULSIVE SHOCK THERAPY BY MAGNESIUM SULFATE

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Traumatic complications in the form of fractures of the spinal vertebrae and extremities represent a serious drawback to convulsive shock therapy. To date, none of the measures suggested to prevent complications have been accepted as entirely prophylactic or entirely practical. The essential problem in convulsive therapy is to eliminate or soften the severity of the tonic muscular contractions which cause skeletal fractures by direct muscle pull. Various chemical agents have been used to nullify the severity of the convulsion. These agents act by blocking the peripheral neuromuscular mechanism and thus produce peripheral motor paralysis of all striated musculature. Bennett,[1] who was the first to apply the principle of curarization in shock therapy, demonstrated that an aqueous extract of crude curare could be standardized and given safely prior to metrazol convulsive therapy. He has reported and demonstrated that he can produce with the intravenous administration of curare a flaccid motor paralysis sufficient to soften the metrazol convulsion. Burman[2] reported on the similar action of curare and erythroidine in various neurologic disorders associated with pyramidal and extrapyramidal motor dysfunction. Rosen, Cameron and Ziegler[3] used an aqueous solution of beta erythroidine hydrochloride with success in the prevention of traumatic complications in metrazol convulsions.

However, the chemical agents thus far suggested to produce a curare-like effect prior to convulsive therapy are not entirely satisfactory, owing to particular difficulties associated with each method. The col-

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1. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**:322 (Jan. 27) 1940.

2. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**:307 (Feb.) 1939.

3. Rosen, S. R.; Cameron, D. E., and Ziegler, J. B.: The Prevention of Metrazol Fractures by Beta-Erythroidine Hydrochloride, Psychiatric Quart. **14**: 477, 1940.

lection and preparation of crude curare present a difficult and expensive task. Furthermore, there is no specific antidote for curare poisoning, and the hazard of overdose always confronts the therapeutist. In the use of beta erythroidine hydrochloride the authors report the occasional occurrence of severe postconvulsive respiratory depression which necessitates artificial respiration or the use of prostigmine methylsulfate intravenously. They also found that postconvulsive confusion is prolonged in some cases.

My associates and I have endeavored to find a chemical agent which would fulfil the following criteria: (1) a curare-like drug whose toxic effect on the central nervous system is minimal and whose margin of safety in administration is great; (2) a drug which has a specific antidote, if the need arises, and (3) a drug the preparation of which is relatively simple. We have been particularly interested in magnesium, especially magnesium sulfate, and now feel that it meets, as nearly as possible, the criteria which we have set for a practical substitute for crude curare. In most of the cases in the present study in which magnesium sulfate was employed prior to injection of metrazol, it produced a definite transient paresis of the skeletal musculature, similar to the action of curare. The flaccid paresis of muscles produced in all our cases was sufficient to protect the patient from fractures. Not only were the convulsions softened but in some of the treatments the tonic muscular contractions induced by metrazol were abolished.

Meltzer and Auer [4] attributed the reduction in bodily activity resulting from the parenteral injection of magnesium salts to a narcosis of the central nervous system. Guthrie and Ryan [5] emphasized the action of magnesium salts on the peripheral neuromuscular system and claimed that the depression of activity results from a paralysis like that produced by curare. In spite of the demonstration by Peck and Meltzer [6] of anesthesia without motor paralysis in man following intravenous injections of magnesium sulfate, the theory of peripheral action has had continued support.[7] Hoff, Smith and Winkler [8] attempted to determine

4. Meltzer, S. J., and Auer, J.: Physiological and Pharmacological Studies of Magnesium Salts: I. General Anesthesia by Subcutaneous Injections, Am. J. Physiol. **14**:366, 1905; II. The Toxicity of Intravenous Injections, ibid. **15**:389, 1906.

5. Guthrie, C. C., and Ryan, A. H.: On the Alleged Specific Anesthetic Properties of Magnesium Salts, Am. J. Physiol. **26**:329, 1910.

6. Peck, C. H., and Meltzer, S. J.: Anesthesia in Human Beings by Intravenous Injections of Magnesium Sulphate, J. A. M. A. **67**:1131 (Oct. 14) 1916.

7. Wiki, B.: De l'action pharmacodynamique du magnésium, Rev. méd. de la Suisse Rom. **54**:973, 1934; abstracted, Ber. ü. d. ges. Physiol. **84**:319, 1935.

8. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: Effects of Magnesium on the Nervous System in Relation to Its Concentration in Serum, Am. J. Physiol. **130**:292, 1940.

the relation between the concentration of magnesium in the serum, on the one hand, and the change in reflex activity and in neuromuscular transmission, on the other. They used decerebrate cats, with supplementary experiments on neuromuscular transmission in animals anesthetized with sodium amytal. Their experimental evidence led them to the conclusion that the reflexes in their animals failed because of neuromuscular block rather than because of an action of magnesium on the central nervous system.

On the basis of the work of those experimenters who demonstrated the curare-like action of magnesium excess, we utilized the sulfate salt of magnesium prior to metrazol therapy. Clinically, we have been able to substantiate their conclusions. The demonstration by Peck and Meltzer that anesthesia may be produced in man by the injection of magnesium sulfate is unequivocal evidence that a central effect does exist. They made the observation that the central effect may or may not be accompanied by pronounced paralysis of the endings of the motor nerves of a great part of all skeletal muscles. However, they stated that the central effect could be attained with a smaller dose than that which was required for paralysis of motor nerve endings. The latter observation is not in accord with our experience. Curare-like effects are first observed before any profound disturbances in the central nervous system become evident. We have not tried to produce anesthesia in our patients and hence have failed to observe any disturbance of consciousness. Peck and Meltzer used large amounts of a solution of magnesium sulfate to achieve their results. In 1 of their patients they infused 394 cc. of a 6 per cent solution in forty-eight minutes. We have never injected more than 30 cc. of the 25 per cent solution which we employed. A transient paresis of muscle similar to the effect of curare is produced with the concentration and dosage we have used. The flaccid paresis of muscles is sufficient to protect the patient from fractures.

## METHOD

Two hundred and fifty-six magnesium sulfate–metrazol treatments were administered to 23 patients, ranging in age from 18 to 64 years. Both sexes were about equally represented in the group.

The patient reclines on a firm, flat surface. The patient's back is kept in hyperextension by means of a firm pillow or a folded blanket placed between the scapulas. From 25 to 30 cc.[9] of a 25 per cent sterile aqueous solution of magnesium sulfate is injected as rapidly as possible. Approximately 0.1 to 0.12 Gm. of magnesium sulfate per kilogram of body weight is found sufficient to produce some degree of muscular

9. A 25 per cent solution of magnesium sulfate, chemically pure, in distilled water is prepared, stored in flasks and autoclaved. This method provides, at practically negligible cost, a solution that gives satisfactory results.

paresis. The physiologic effects of the drug appear in the following order: Immediately, at the onset of the injection, the patient complains of a marked sensation of "heat." This subjective complaint is associated with flushing of the face and neck and diaphoresis. Subjective heaviness of the eyelids and bilateral ptosis occur rapidly. There are now weakness of the muscles of the neck and some difficulty in raising the head. Speech becomes slow, hesitant and slurred. At this point there is marked paresis of the hand grips. The appearance of the subject at this stage is that of a patient with severe myasthenia gravis. When this effect has been produced (usually within one to three minutes after the intravenous injection of magnesium sulfate), the estimated convulsant dose of metrazol is given. The curare-like effect wears off within three to six minutes after it is reached. Hence it is imperative to inject the metrazol immediately at the height of body relaxation in order to get maximum "softening" of the subsequent convulsion. A good indication of this point is marked ptosis of the eyelids. The usual metrazol convulsion supervenes, but with much less severity of tonic and clonic contractions. With return of consciousness the effects of the magnesium sulfate have disappeared.

In order to overcome any untoward depressive effects of magnesium which might occur, a sterile aqueous solution of 10 per cent calcium chloride is kept on the treatment tray. Calcium has been shown to have an action on the same mechanisms, both central and peripheral, which is antagonistic to the depressive effect of magnesium.[10] There has been no occasion in our series of treatments to use this preparation.

## COMMENT

In 256 magnesium sulfate–metrazol treatments there have been no serious complications. Roentgenograms taken of the spines of the patients before and after treatment revealed no evidence of spinal fractures. The effectiveness of convulsive therapy was found to remain the same. The treatment was administered to patients of all ages, with no deleterious effects. Some of the patients were distressed by a sensation of intense "heat" as the magnesium was injected. This sensation results from the peripheral vasodilator effect of magnesium.[11] No severe cardiac dysfunction was observed clinically after the treatment. In a future study we plan to obtain electrocardiographic records

10. Bryant, G. W.; Lehman, G., and Knoefel, P. K.: The Action of Magnesium on the Central Nervous System and Its Antagonism by Calcium, J. Physiol. & Pharmacol. **65**:318, 1939.

11. Haury, V. G.: The Effect of Intravenous Injections of Magnesium Sulphate on the Vascular System, J. Pharmacol. & Exper. Therap. **65**:453, 1939; The Effect of Intravenous Injections of Magnesium Sulphate on the Volume of the Extremities, J. Lab. & Clin. Med. **24**:951, 1939.

from patients treated by the magnesium sulfate–metrazol method. Bernstein and Simpkins [12] studied the electrocardiographic tracings of 100 patients for the effect of 10 cc. of a 10 per cent aqueous solution of magnesium sulfate injected intravenously. Thirty-four of these patients were apparently free of cardiovascular disease, whereas 66 presented various forms and degrees of severe cardiac disease. A study of the tracings led the authors to conclude that intravenous injections of magnesium sulfate in the dosage they employed exerted no deleterious effect on the human heart. In 2 cases, in which more than 25 cc. of the 25 per cent solution of magnesium sulfate was used, the period of apnea after the convulsion was prolonged. We have learned that our dose of magnesium or metrazol was too high in these cases. We have felt that one should aim not for complete motor paralysis in convulsive therapy, but for enough muscular relaxation to achieve a "softened" convulsion. From our experience, we believe the drug is safe if carefully administered.

## CONCLUSIONS

1. Solution of magnesium sulfate, a drug with a curare-like action, has proved to be satisfactory for prevention of traumatic complications in convulsive shock therapy.

2. The dosage of magnesium sulfate is more accurate and easier to gage with relation to the patient than that of curare, as the margin of safety is much greater. The preparation of this drug is relatively simple and economical.

12. Bernstein, M., and Simpkins, S.: Magnesium: The Effects of Intravenous Injections on the Human Heart, J. Lab. & Clin. Med. **25**:131, 1939.

# PROGNOSTIC VALUE OF INTRAVENOUS ADMINISTRATION OF SODIUM AMYTAL IN CASES OF SCHIZOPHRENIA

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The purpose of this communication is to report on the relation of the types of behavior observed and verbal productions elicited in interviews produced by the intravenous administration of sodium amytal (sodium isoamylethylbarbiturate) in subnarcotic doses to the course and clinical status of patients suffering from schizophrenia. This relation is of value in determining the prognosis for the individual patient.

Sodium amytal has been used in the treatment of the psychoses since 1930, when it was introduced by Bleckwenn.[1] Although he described short lucid periods during the administration of the drug, the changes which he noted were particularly prominent after the initial period of sleep. Later Lindemann [2] and Lindemann and Malamud [3] showed that similar, and equally prolonged, temporary remissions could be produced by intravenous doses of the drug which were insufficient to cause sleep. In brief, they found a striking change from a resistive, seclusive attitude to one of friendliness and emotional warmth, frequently associated with feelings of well-being, and a desire to retain the condition produced by the drug. Although there was directly no influence on delusions or hallucinations, the remarkable improvement in contact with the environment, both as to communicativeness and warmth of emotion, led frequently to a revealing of hidden thoughts and allowed a search for and a discussion of the patient's experiences and attitudes. The intravenous use of sodium amytal has come to be accepted by many as a useful tool in the psychotherapeutic approach to schizophrenia.

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From the Iowa State Psychopathic Hospital.

Read, in part, on Dec. 5, 1940 at a meeting of the Illinois Psychiatric Society, Chicago.

1. Bleckwenn, W. J.: Narcosis as Therapy in Neuropsychiatric Conditions, J. A. M. A. **95**:1168 (Oct. 18) 1930.

2. Lindemann, E.: Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, Am. J. Psychiat. **11**:1083 (May) 1932.

3. Lindemann, E., and Malamud, W.: Experimental Analysis of the Psychopathological Effects of Intoxicating Drugs, Am. J. Psychiat. **13**:853 (Jan.) 1934.

Harris, Horwitz and Milch [4] showed that the type of response to intravenous administration of sodium amytal was of prognostic value when insulin shock therapy was employed. In their study of 55 cases, they obtained a favorable therapeutic result in 77 per cent of the patients showing an ameliorating reaction to the injection of sodium amytal. On the other hand, 64 per cent of those having a poor reaction to sodium amytal failed to respond therapeutically. Their report had been anticipated [5] and has been confirmed.[6]

The purpose of the present study was to evaluate sodium amytal as an agent in the prognosis of schizophrenia. This was done by analyzing the effect of the drug on patients suffering from the disease and its relationship to the clinical status of groups of patients treated in various ways whose course had been followed over an extended period.

## METHOD

Intravenous injection of sodium amytal has been used as an aid in diagnosis or in psychotherapy of schizophrenia at the Iowa State Psychopathic Hospital since its introduction, in 1930. The technic of administration was uniform.

The patient lay comfortably on a couch or bed. A fresh solution of crystalline sodium amytal, containing 0.065 Gm. (1 grain) per cubic centimeter of distilled water, was injected intravenously at a speed not exceeding 1 cc. per minute. After the injection of 2 or 3 cc. conversation was begun, the injection continuing until the patient's communicativeness had reached a maximum. An attempt was made to control the amount of drug given so that sleep was not produced. The amount of drug necessary to obtain the maximum response varied from 0.195 to 0.52 Gm. (3 to 8 grains). The number of injections given any one patient varied considerably and depended on the type of response; frequently the better the response the more injections were given for therapeutic endeavor. The type of response obtained on the first injection is utilized primarily for evaluation, although the importance of change in responsiveness of the patient to repeated injections will be indicated.

During the years 1930 to 1938, inclusive, 427 patients in the hospital were found to be suffering with schizophrenia. The patients admitted from 1930 to 1936, inclusive, were reexamined during April 1938, by the psychiatrists of the hospital, and their clinical status determined. The

4. Harris, M. M.; Horwitz, W. A., and Milch, E. A.: Regarding Sodium Amytal as a Prognostic Aid in Insulin and Metrazol Shock Therapy of Mental Patients, Am. J. Psychiat. **96**:327 (Sept.) 1939.

5. Berrington, A. P.: Psychopharmacologic Study of Schizophrenia, with Particular Reference to Mode of Action of Cardiazol, Sodium Amytal and Alcohol in Schizophrenic Stupor, J. Ment. Sc. **85**:406 (May) 1939.

6. Heilbrunn, G., and Sternlieb, R.: Insulin Therapy of Schizophrenia in the Elgin State Hospital, with Special Reference to Relapses and Failures, Am. J. Psychiat. **96**:1203 (March) 1940.

results of that prognostic study were published by Malamud and Render.[7] The clinical condition of the patients admitted during 1937 and 1938 who were suitable for this study was evaluated by a staff psychiatrist during December 1939, and again in June 1940.

On the basis of the clinical status the patients were divided into four subgroups, as follows:

1. Completely Recovered: The patient was living in the community and practicing his previous occupation, or one at about the same level. He was adjusting as he did before the onset of the disease, and there was complete absence of psychiatric symptoms.

2. Socially Recovered: The patient was living in the community and adjusting well socially, was considered as normal by his associates and was supporting himself independently, but there were signs of minor defects, mainly in affect.

3. Improved with Defect: The patient was either living in the community or in a hospital, was able to work, but at a lower level than previously, and showed definite defect.

4. Unimproved: The patient showed no improvement, or the process had continued to deterioration.

Since the follow-up studies on these patients were complete and their present condition known, the records were reviewed with the purpose of selecting those who had received sodium amytal intravenously. Only those cases could be used in which the effect of the sodium amytal was described in detail. In many cases the verbatim productions of the patients recorded by a stenographer at the time of the interview were available for study.

In the evaluation of the effect of the drug considerable difficulty was experienced. The attempt was made to estimate the degree of involvement of certain characteristics of the disease as emphasized by Bleuler while the patient was under the effect of the drug. Although the independent appraisal of these characteristics was utilized primarily, the change in the mental status produced by the drug was taken into consideration. Each characteristic was evaluated separately. The characteristics selected were:

1. Disturbances of affect, such as inadequacy and inappropriateness.

2. Disturbances in association processes, such as shortness, vagueness and lack of logical relationship.

3. Disturbances in attention, such as shifts and gaps without apparent reason.

4. Disturbances in contact with the outside world.

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7. Malamud, W., and Render, N.: Course and Prognosis in Schizophrenia, Am. J. Psychiat. **95**:1039 (March) 1939.

5. Abnormal mental content, such as delusions and hallucinations.

6. Distortion of insight.

Each patient was then assigned to one of three groups, depending on the degree to which the reaction approximated normality with respect to the characteristics selected. Three of the factors enumerated seemed less important than the others. In most cases, at least those in which stupor or sleep did not follow injection of the drug, the attention defects and the contact with the environment improved considerably, out of proportion to the other factors. On the other hand, when most of the factors were near normal, the expression of abnormal subjective experiences tended to continue. The factors that were depended on most in the evaluation were thus: (1) the state of the affect; (2) the associations, and (3) the degree of insight.

On the basis of the reaction, the patients were classified as follows:

*Group with Good Reactions.*—The affect was warm and evaluated as appropriate to the thought contact, the associations were normal and the insight was relatively good.

*Group with Moderate Reactions.*—Affect, associations and insight approached the normal and showed definite improvement after administration of the drug, but abnormalities were still evident.

*Group with Poor Reactions.*—The mental content showed considerable defect in respect to the three factors, in spite of good attention and contact with the outside world, or there was complete failure of response.

## RESULTS

One hundred patients comprise the basis for this report. They were divided into two groups on the basis of the difference in therapy. One group of 70 patients was treated by the conservative, nonshock, psychotherapeutic method. This method has been described in detail by Malamud and Miller.[8] The other group of 30 patients received either insulin or mecholyl (acetylbetamethylcholine chloride)[9] therapy.

In table 1 is presented the relative proportion of the 70 patients treated conservatively who showed clinical improvement.

Fourteen per cent showed complete recovery, 9 per cent social recovery, 7 per cent improvement and 70 per cent no improvement. Because these patients were selected arbitrarily on the basis of having received sodium amytal intravenously, it may be thought that the case material does not represent a typical cross section of the schizophrenic population. This would seem possible, as the material was skewed

8. Malamud, W., and Miller, W. R.: Psychotherapy in the Schizophrenias, Am. J. Psychiat. **11**:457 (Nov.) 1931.

9. Malamud, W., and Gottlieb, J. S.: Present Day Trends in the Treatment of Schizophrenia, J. Missouri M. A. **37**:1 (Jan.) 1940.

to the side of uncommunicativeness and lack of contact with the outside world, since the patients who were mute, stuporous, resistive, seclusive and excited were more likely to have received the drug. A comparison with the results reported by Malamud and Render [7] in 309 cases revealed that the relative improvement for our group was slightly less than that for the larger schizophrenic population. According to their figures, 17 per cent showed complete recovery, 11 per cent social

TABLE 1.—*Analysis, Irrespective of Effect of Sodium Amytal, of Groups Based on Final Clinical Status in Relation to Age, Sex, Onset, Length of Illness, Type of Schizophrenia and Length of Follow-Up Study for Patients Treated by Nonshock Methods*

| | Final Clinical Status | | | | |
|---|---|---|---|---|---|
| | Complete Recovery | Social Recovery | Improved | Unimproved | Total |
| Number | 10 (14%) | 6 (9%) | 5 (7%) | 49 (70%) | 70 (100%) |
| Age | | | | | |
| Minimum | 14 | 18 | 20 | 16 | 14 |
| Mean | 23.0 | 24.8 | 27.0 | 26.8 | 26.1 |
| Maximum | 35 | 37 | 37 | 41 | 41 |
| Sex | | | | | |
| Male | 4 (40%) | 4 (67%) | 4 (80%) | 25 (51%) | 37 (53%) |
| Female | 6 (60%) | 2 (33%) | 1 (20%) | 24 (49%) | 33 (47%) |
| Onset | | | | | |
| Acute | 5 (50%) | 2 (33%) | 1 (20%) | 7 (14%) | 15 (21%) |
| Gradual | 5 (50%) | 4 (67%) | 4 (80%) | 42 (86%) | 55 (79%) |
| Length of illness before hospitalization | | | | | |
| 6 months | 8 (80%) | 5 (84%) | 1 (20%) | 18 (37%) | 32 (46%) |
| 1 year | 1 (10%) | ..... | 1 (20%) | 6 (12%) | 8 (11%) |
| 2 years | 1 (10%) | ..... | 1 (20%) | 7 (14%) | 9 (13%) |
| 5 years | ..... | 1 (16%) | 2 (40%) | 13 (27%) | 16 (23%) |
| Plus 5 years | ..... | ..... | ..... | 5 (10%) | 5 (7%) |
| Subgroup | | | | | |
| Catatonic | 2 (20%) | ..... | ..... | 9 (18%) | 11 (16%) |
| Paranoid | 2 (20%) | 1 (16%) | ..... | 6 (12%) | 9 (13%) |
| Simple | 1 (10%) | ..... | 2 (40%) | 6 (12%) | 9 (13%) |
| Hebephrenic | ..... | 1 (16%) | 3 (60%) | 16 (33%) | 20 (28%) |
| Unclassified | 5 (50%) | 4 (67%) | ..... | 12 (25%) | 21 (30%) |
| Years of follow-up observation | | | | | |
| Eight | ..... | ..... | ..... | 2 (4%) | 2 (3%) |
| Seven | 3 (30%) | ..... | ..... | 2 (4%) | 5 (7%) |
| Six | 2 (20%) | ..... | ..... | 8 (16%) | 10 (14%) |
| Five | 1 (10%) | ..... | ..... | 9 (19%) | 10 (14%) |
| Four | 1 (10%) | ..... | ..... | 3 (6%) | 4 (6%) |
| Three | 1 (10%) | ..... | 1 (20%) | 7 (14%) | 9 (13%) |
| Two | 2 (20%) | 3 (50%) | 1 (20%) | 5 (10%) | 11 (16%) |
| One | ..... | 3 (50%) | 3 (60%) | 13 (27%) | 19 (27%) |

recovery, 7 per cent improvement and 56 per cent no improvement and 7 per cent died. The differences, which are slight, do not seem sufficient to invalidate our data as representative of the entire schizophrenic population.

Table 1 also presents an analysis of the groups based on the observed clinical status as related to age, sex, type of onset, length of illness before hospitalization, type of schizophrenia and number of years of follow-up observation. There were no significant differences for the factors of age or sex. A larger proportion of patients showing complete recovery had acute onsets. The patients ill less than six

months had a much better chance of recovery than those whose illnesses were of longer duration. Because of the relatively high incidence of patients in this series with illnesses of short duration, the percentage of patients in the subgroup of unclassified schizophrenia was high. In many instances the disease process had not continued long enough for its classification under another of the subgroups to become clear. The distribution in the follow-up survey showed that in 43 per cent of the cases the illness was of one or two years' duration. This implies that there probably will be further shifts in the degree of clinical improvement.

In table 2 is presented the relation of the types of reaction produced by the intravenous injection of sodium amytal to the clinical status of the patients treated by nonshock methods. Only 10 of the 70 patients had good reactions: of these 6, or 60 per cent, made complete recoveries, and 4, or 40 per cent, made social recoveries. No patient failed to improve. Thirteen patients had moderate reactions. Of these, 4, or 31

TABLE 2.—*Relation of Reactions Following Intravenous Injection of Sodium Amytal to Final Clinical Status of Patients Treated by Nonshock Methods*

| Reaction to Sodium Amytal | | Final Clinical Status | | | |
|---|---|---|---|---|---|
| | Number | Complete Recovery | Social Recovery | Improved | Unimproved |
| Good | 10 (14%) | 6 (60%) | 4 (40%) | ..... | ..... |
| Moderate | 13 (19%) | 4 (31%) | 1 (7%) | 3 (23%) | 5 (39%) |
| Poor | 47 (67%) | ..... | 1 (2%) | 2 (4%) | 44 (94%) |
| Total | 70 (100%) | 10 (14%) | 6 (9%) | 5 (7%) | 49 (70%) |

per cent, made complete recoveries; 1, or 7 per cent, made a social recovery; 3, or 23 per cent, improved, and 5, or 39 per cent, were unimproved. With a moderate reaction to sodium amytal, there was a fairly even distribution in the observed clinical status. Forty-seven patients had poor reactions; none made a complete recovery; 1, or 2 per cent, made a social recovery, 2, or 4 per cent, improved, and 44, or 94 per cent, were unimproved. A poor reaction almost invariably indicated failure to improve or deterioration. From these data it seemed safe to conclude that the type of reaction to sodium amytal was indicative of the prognosis for a given patient when conservative psychotherapeutic treatment was given.

The reactions produced by sodium amytal in the second group, that of 30 patients treated by either the insulin or the mecholyl [9] method, may now be compared. Although the series was small, the trends were clearly defined. As table 2 shows for those treated conservatively, table 3 presents the relation of the types of reaction following the intravenous injection of sodium amytal to the observed clinical status of patients treated by shock methods. Relatively more improvement is indicated in

this group than in the group treated by nonshock methods: Twenty per cent made a complete recovery, 27 per cent made a social recovery, 13 per cent improved and 40 per cent did not improve. However, since the length of follow-up observation was one to three years, there may be further shifts in the direction of relapse in the patient's final condition.

Table 3 shows a general shift in the direction of improvement of patients receiving shock therapy. As is shown in table 2, if the reaction to the drug was good, the final condition of the patient was complete or social recovery. If the reaction was moderate, treatment by one of the shock methods gave the patient approximately the same chance of

TABLE 3.—*Relation of Reactions Following Intravenous Injection of Sodium Amytal to Final Clinical Status of Patients Treated by Shock (Insulin and Mecholyl) Methods*

| Reaction to Sodium Amytal | | Final Clinical Status | | | |
|---|---|---|---|---|---|
| | Number | Complete Recovery | Social Recovery | Improved | Unimproved |
| Good | 5 (17%) | 2 (40%) | 3 (60%) | ..... | ..... |
| Moderate | 11 (37%) | 3 (27%) | 2 (19%) | 3 (27%) | 3 (27%) |
| Poor | 14 (46%) | 1 (7%) | 3 (21%) | 1 (7%) | 9 (65%) |
| Total | 30 (100%) | 6 (20%) | 8 (27%) | 4 (13%) | 12 (40%) |

TABLE 4.—*Relation of Reactions Following Intravenous Injection of Sodium Amytal to Final Clinical Status of Entire Group of 100 Patients*

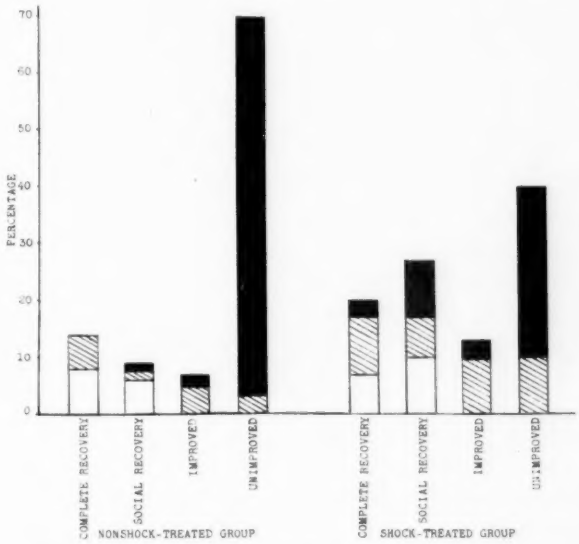
| Reaction to Sodium Amytal | | Final Clinical Status | | | |
|---|---|---|---|---|---|
| | Number | Complete Recovery | Social Recovery | Improved | Unimproved |
| Good | 15 (15%) | 8 (53%) | 7 (47%) | ..... | ..... |
| Moderate | 24 (24%) | 7 (29%) | 3 (13%) | 6 (25%) | 8 (33%) |
| Poor | 61 (61%) | 1 (2%) | 4 (6%) | 3 (5%) | 53 (87%) |
| Total | 100 (100%) | 16 (16%) | 14 (14%) | 9 (9%) | 61 (61%) |

improvement as treatment by a nonshock method: Forty-six per cent were either completely or socially recovered, as compared with 38 per cent of those treated without shock. If the reaction was poor, shock therapy offered hope for improvement: Twenty-eight per cent had complete or social recovery, while without shock treatment only 2 per cent improved to the same degree.

In table 4 is presented the relationship of the types of reaction produced by the intravenous injection of sodium amytal to the clinical status for the entire group of 100 patients who comprised the study. The table shows that all of the patients having a good reaction to sodium

amytal recovered, while the vast majority of the patients having a poor reaction to the drug failed to improve.

The accompanying chart emphasizes further the comparison of the results found in the two differently treated groups. It reveals graphically the percentage of patients in each of the clinical groups as determined by follow-up examination. The first half of the distribution is for the 70 patients treated conservatively; the last half is for the 30 patients treated with insulin or mecholyl. Each subgroup is then further divided according to the percentage of good, moderate or poor reactions to sodium amytal. Several facts are apparent from this chart. The first




Comparison by percentages of the relative degrees of clinical improvement for groups of schizophrenic patients treated by the nonshock and the shock methods. The first half represents the 70 patients treated psychotherapeutically; the last, half, the 30 patients treated with insulin or mecholyl. For further comparison, each subgroup, represented by the clinical status at follow-up examination, is further divided according to the percentage of good, moderate or poor reactions to sodium amytal. A good reaction to amytal is represented by a blank area; a moderate reaction, by a cross-hatched area, and a poor reaction, by a solid black area.

is the higher percentage of completely and socially recovered patients in the group receiving shock therapy. The second is the relatively greater percentage of moderate reactions to sodium amytal in the shock-treated group than in the group treated more conservatively, the figures being 37 and 10 per cent, respectively. An implication is that a larger pro-

portion of the patients in the shock-treated group would have better prognoses even without shock therapy. This difference would seem to explain in part the relatively larger percentage of improvement in the clinical status of patients treated by shock. However, this factor is inadequate to explain entirely the differences in final outcome between the two groups. The most significant fact is the relatively greater proportion of patients with poor reactions to sodium amytal who when treated with shock methods showed improvement of varying degrees: 35 per cent, as compared with 6 per cent for the more conservatively treated patients. This may be interpreted as indicating that the shock therapies hold out hope of improvement for a small proportion of those patients who have poor reactions to sodium amytal and who fail to gain the same relative amount of benefit from the more conservative methods of therapy.

Since many of the patients in both the group treated conservatively and the group treated by shock received subsequent injections of sodium amytal, a study of these reactions became pertinent.

Of the 15 patients who had good reactions to sodium amytal, 8 received the drug from two to fourteen times. The subsequent reactions of all patients, with 1 exception, were similar to the initial response. For all but that patient the final status was either complete or social recovery. The case of the exceptional patient is pertinent to the thesis. A 25 year old single man was admitted to the hospital on March 18, 1936. The illness had been of insidious onset, of at least two years' duration. The symptoms had steadily increased in severity, until at the time of admission he was in a profound catatonic stupor. The intravenous injection of sodium amytal resulted in a dramatic change, the patient then closely approximating normal in all of his characteristics. After the injection the patient did not relapse to the same degree of stupor as formerly. Three more injections of the drug were given at weekly intervals, with similar reactions. This was followed by slow, progressive clinical improvement, permitting his discharge on April 16, 1936. At that time he was free from symptoms and was able to return to his previous level of socialization. He remained well for about one year, when he suffered a relapse and was returned to the hospital, on April 5. Again, he was in a catatonic stupor, which gradually changed during his period of hospitalization, with hebephrenic features becoming prominent. Intravenous injections of sodium amytal then had no effect on the symptoms, and the reaction was poor. He was treated by intrathecal injections of mecholyl, but continued to deteriorate. Finally he was transferred, on August 19, 1937, to a state hospital, where he remains to date.[10] The change in the reaction to sodium amytal in this case would seem to be indicative of the change in the course of the psychosis.

Of the 24 patients who had moderate reactions, 10 received the drug on subsequent occasions. Eight had similar reactions. The clinical status of these patients at follow-up examination was as follows: Two were completely recov-

10. For the statistical study, this patient was included in the shock-treated group having a poor reaction to sodium amytal.

ered, 1 was socially recovered, 3 were improved, and 2 were unimproved. The ninth patient showed a change from a moderate reaction to a good one, the clinical status being complete recovery. The case of the tenth patient, a 17 year old girl, is of particular interest. She was admitted to the hospital on Aug. 19, 1931, in a catatonic stupor of eight months' duration. During her stay, until Feb. 18, 1932, she received five injections of sodium amytal. The first reaction was classified as moderate. On each subsequent injection the response improved, until the fourth was classified as good. The patient's clinical condition gradually improved, until she was free from symptoms at the time of discharge. She remained well until a catatonic stupor again developed, one month before her second admission, on Aug. 13, 1937. The intravenous injection of sodium amytal then produced only an increase in volubility, without any significant changes in either the affect or the associations. The reaction was considered poor. She was discharged as unimproved to return to her parents on Sept. 7, 1937. As they were unable to care for her adequately, she was readmitted on Jan. 3, 1938. Sodium amytal was administered on two occasions, the response to each injection being simply an increase in the severity of the stuporous state. Finally, on Feb. 16, 1938, the patient was transferred to a state hospital, where she remains to the present, in a dilapidated, deteriorated state. Again, in this case, as in the one previously cited, the various reactions to sodium amytal seemed to indicate the course of the psychosis.

Of the 61 patients who had poor reactions, 22 received subsequent injections of the drug. Twenty-one had either similar or poorer reactions, the latter being characterized by an increase in stupor or drowsiness; of these, 1 completely recovered, 2 recovered socially, 1 improved and 17 failed to improve. The case of the patient, a single woman aged 25, whose reaction to sodium amytal improved, changing from a poor to a good response, may be mentioned in brief. She entered the hospital in an acutely excited state, of two weeks' duration. The initial reaction to sodium amytal was poor, simply bringing out the characteristics of the disease. She was treated with intrathecal injections of mecholyl, and after a series of twenty injections, during which time there was only slight clinical improvement, sodium amytal was given again. The reaction was dramatic and brought the patient into good contact with the situation. The affect became friendly and warm; the associations, which had been bizarre, normal, and the insight into her numerous delusions and hallucinations good. The subsequent course of the patient was one of steady improvement, until she was showing only slight residuals of the disease. The evaluation of her condition at follow-up examination was one of social recovery. It would seem, therefore, that the type of reaction to intravenous administration of sodium amytal is indicative, at least in some cases, of the relatively immediate future course of the psychosis.

## COMMENT

The data show clearly that either a good or a poor reaction to the intravenous injection of sodium amytal is indicative of the prognosis for a given schizophrenic patient. This becomes obviously of great usefulness. Although group analysis of clinical material has resulted in a fair amount of agreement among investigators in regard to certain factors as indicative of the prognosis, it is recognized, nevertheless, that

the factors of importance in a group evaluation become less reliable when applied in a given case. It is the common experience with schizophrenic patients presenting favorable clinical signs that they continue to deterioration, while the reverse, although less often, occasionally occurs. The intravenous injection of sodium amytal, a simple and harmless procedure, gives a quick and fairly reliable prognostic appraisal for a large percentage of schizophrenic patients.

For a small percentage of patients with good or poor reactions, the initial injection may not offer an entirely reliable prognosis and subsequent injections may be necessary in order to follow the course of the illness. Although subsequent reactions are usually of the same order as the initial ones, they need not be. The cases reported illustrate that subsequent responses may change by either improving or becoming worse. This reversibility seems of considerable importance, for it implies that for these few patients the reaction to the drug can serve only as an interim index to the course of the psychosis.

Nevertheless, the consistency and reliability of the data in the conservatively treated group allow use of the reaction to the drug as a measure of the efficacy of the prevailing therapy. The data presented indicate that if the patient has a good response to sodium amytal, he will recover socially or completely, regardless of the type of therapy. The data also show that a poor response to the drug indicates failure of improvement when the patient is treated by nonshock methods. A significant percentage of the patients who had poor responses showed clinical improvement of varying degrees when treated by shock (insulin or mecholyl). This may be interpreted as supporting the value of these methods. However, it must be borne in mind that schizophrenia, being a disease of remissions and exacerbations, is difficult to evaluate in a period of less than five years.[7] Consequently, there may be further shifting in the clinical status of the shock-treated patients in the present series, for the follow-up period varied from one to three years.

The close relationship between the type of reaction produced by sodium amytal and the course of the illness may present a method of approach to the elucidation of the pathologic physiology of the disease. If the site and mode of action of the drug in the central nervous system were definitely known, an abnormality of that area might be implied. Unfortunately, the area of the central nervous system affected has not been conclusively established. Some investigators believe that the site of action is primarily in the cortex.[11] However, the majority believe

11. Kleitman, N.: Sleep and Wakefulness, Chicago, University of Chicago Press, 1939, chap. 29. Tatum, A. L.: The Pharmacology of Barbiturates, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1940, vol. 2.

that the barbiturates act at subcortical levels and that the action may be localized primarily in the hypothalamus.[11] If the action of the drug is on the cells of the hypothalamus, the observations reported here might lend support to the contentions of those who believe that schizophrenia is a disease in which the hypothalamus is in some wise involved. Regardless of this, one is warranted in the hypothesis that the type of clinical response produced by the drug is an index to the magnitude of involvement of the abnormal functioning portion of the brain and that in the majority of cases it may be indicative of the reversibility of the process at the time of the drug's administration. Further investigations which may throw light on this problem are in progress.

## SUMMARY

One hundred patients suffering with schizophrenia who received sodium amytal intravenously have been followed from one to eight years.

Of the 70 patients treated by nonshock methods, 10 had previously shown good reactions to sodium amytal and made either a complete or a social recovery. Of the 47 patients who had shown poor reactions to sodium amytal, 44 failed to improve or continued to deteriorate.

Of the 30 patients treated by the insulin or mecholyl methods, 5 had shown good reactions to sodium amytal and made either a complete or a social recovery. Of the 14 patients who had shown poor reactions to sodium amytal, 9 were unimproved, while 4 made either a complete or a social recovery.

Of the entire group of 100 patients forming the basis of this study, 15 had shown good reactions to sodium amytal, and all of these patients made either a complete or a social recovery. Of the 61 patients who had shown poor reactions to sodium amytal, 53 were unimproved.

Repeated intravenous injections of sodium amytal as indicated by the type of response are helpful in following the course of the psychosis.

## CONCLUSIONS

The type of response obtained by the intravenous injection of sodium amytal is of distinct aid in the evaluation of the prognosis for a given schizophrenic patient. The more closely the patient's behavior approaches normal under the influence of the drug, the better the prognosis. The reactions produced by the drug may be helpful in the evaluation of new types of therapy.

## DISCUSSION

DR. MAXWELL GITELSON, Chicago: Before proceeding to that part of my discussion in which I am chiefly interested, I should like to raise a question as to the statistical validity of the authors' thesis, despite the fact that the thesis itself

impresses me with its internal consistency. With respect to the positive prognostic value of the amytal technic, even though all 15 patients whose reaction was classified as "good" made a complete or a social recovery, the number does not seem sufficiently large to justify a final conclusion. The same criticism would apply to the 24 patients in whom a "moderate" reaction to amytal was observed and of whom only 10 went on to complete or social recovery. The negative predictive value of the amytal technic on the basis of the authors' figures seems much better validated statistically, since 53 of 61 patients with "poor" reactions were clinically unimproved. That is, there seems to be good evidence that a poor experimental reaction is prognostic of a poor clinical outcome, but the corollary would require more definite statistical proof.

It seems to me that the comparison of clinical outcome with experimental response should start with the latter as a basis. It would be more convincing to determine the clinical outcome in 100 cases in which good experimental responses had been obtained and to compare the clinical results with those in 100 cases in which poor experimental responses had been obtained.

Another conclusion which would bear scrutiny from the statistical standpoint is the reference to the "small proportion of those patients who have poor reactions to sodium amytal" but who improve under shock treatment, as they did not under conservative treatment. The authors modify their opinion here by referring to the shorter follow-up period of observation on the shock-treated patients. This modification is necessary in the light of the accumulating statistics on insulin therapy, which are no longer so optimistic as they were. It may be said that the experimental technic described in this paper may help in selection of patients most likely to profit from any reasonable treatment and in reservation of therapeutic efforts to such patients. The fact that some patients with poor experimental reactions recovered under shock treatment does not validate the indiscriminate use of shock therapy, if only because of the small number of such results in this series.

This brings me to the clinical question, which is to me most interesting. It will have been noted that Dr. Gottlieb and Dr. Hope considered a number of criteria for judging the experimental results. It seems significant that they do not include among these criteria the influence exerted by the drug on attention and contact. These capacities, they indicate, were invariably improved by the injection of sodium amytal. The variables which the experiment reveals are with respect to affect, associations and insight. One is really presented here, consequently, with two general factors: one a constant, which seems to be specifically related to the physiologic action of the drug, and the other a variable, which I should like to designate as the factor referring to the status of the ego.

Other drugs than amytal have comparable effects. There have been conflicting reports on alcohol; yet some of the experiences with alcohol both clinically and socially show results similar to those described for amytal in this paper. The point seems to be that amytal, and perhaps other drugs, through their physiologic action influence the psyche so as to bring about such a feeling of well-being and subjective sense of harmony as more fortunate persons have in a less intense, though less transient, form in consequence of placid, deeply rooted, interpersonal relations. I am referring to the fact, brought out by Dr. Allen (Ego Management in the Treatment of a Psychotic Patient, ARCH. NEUROL. & PSYCHIAT. **46**:174 [July] 1941), that the interpersonal disturbances of the schizophrenic patient reflect themselves in disturbances of somatic self awareness and sense of well-

being. This sense of well-being, on the basis of harmonious interpersonal relations, is primitively experienced by the infant in a well integrated relation to the nursing, tending mother.

Therefore, by pharmacologic means there may be brought about a basic experience simulating the normal experience of the person making a normal start in life. It would seem that it is this effect of the drug which serves to uncover the variable reaction which emanates from that part of the psyche which is referred to as the ego. In the clinical situation the profound disturbance, reaching physiologic levels, interferes with contact and attention, both of which are phases of the same thing—capacity for establishing relationships. When, pharmacologically, this capacity is restored, one perceives the variable reaction which emanates from that part of the psyche which has to do with judgment of and response to reality. In other words, the more sophisticated levels of the psyche in which the defense mechanisms develop are brought into clearer focus by effecting transiently a restoration to the deeper, more primitive, levels of the personality.

It is exactly such criteria as Dr. Gottlieb and Dr. Hope have selected for their schizophrenic patients that one looks for in establishing the prognosis in whatever case material one is dealing with. In the treatment of technically nonpsychotic problems, such as those of disturbances in character, one is habitually searching for that part of the ego which is uninvolved in the disturbance and which can stand at some distance from the disturbance. It is one's technical problem in a psychotherapeutic situation to make contact with this intact part of the ego and to enlist its cooperation in the psychotherapeutic process. It seems to me that in the cases presented by the authors the uncovering of relatively intact portions of the ego, which in some cases can be used by the therapeutist to help the patient gain distance from his illness and in other cases seems to enable the patient himself to do so, serves the same purpose in the more malignant disruptions of the personality that skilful, dynamically oriented psychotherapy serves in the clinically less malignant diseases.

In the psychotherapy of the neuroses, the fact is that access to the intact part of the ego, whether present from the beginning or gained technically by the therapeutist, does not solve the problem of the neurosis. Insight without relief is not cure. It becomes only the tool with which a reconstructive psychotherapy is carried on. In the specific cases which the authors cite there is evidence that pharmacologic uncovering of more or less intact aspects of the ego is also not the final answer to the actual treatment of the disease. As they have shown, it gives an outlook, and in some cases a psychotherapeutic lever, but one must know what one is looking at and how to operate the lever.

Despite the questions I have raised with respect to its statistical validity, the procedure described by the authors has inner consistency and is consonant with general clinical knowledge. The usefulness of the procedure rests on the fact that, together with adequate psychotherapeutic skill or by means of medical agents which operate, in ways not altogether clear, on the deeper levels of the personality, one may have a means of improving one's prospects of treating the more malignant diseases of the personality. The injection of amytal contributes knowledge of what one has to work with. But one must do the work.

DR. JACQUES S. GOTTLIEB, Iowa City: I wish to thank Dr. Gitelson for his discussion. Let me say a word about the data presented. I fully realize and agree that conclusions based on a statistical analysis of 100 cases need not be con-

sidered as definitely established. However, since this study was completed, the administration of sodium amytal has become routine in treatment of schizophrenic patients, so that at present we have a large series of patients who are being followed closely. Although time for follow-up study has not been sufficient to permit further conclusions, our clinical impression is that the statements presented here continue to hold true.

It may be well to point out that the patients used in this analysis had received sodium amytal primarily for psychotherapeutic purposes, for they were characterized by being in poor contact with their environment. What was discerned, as Dr. Gitelson remarked, was the degree of preservation of the personality under the impact of the disease; in general, the more intact the personality the better the prognosis. Whether such a prognosis can be made on clinical evidence alone I doubt, and the reaction produced by sodium amytal is, therefore, a useful adjunct in determining the future course of the disease.

# HISTOGENESIS OF SENILE PLAQUES

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The first reference in the literature to the existence of senile plaques was made as early as 1892,[1] but the origin and development of such plaques are still a matter of controversy. No less than twenty different concepts regarding their origin have appeared in the literature. Senile plaques are a characteristic lesion in the brains of persons who during life had suffered from advanced old age, senile dementia or Alzheimer's disease. It has been occasionally claimed that these plaques have been encountered in rare instances in the presence of a few neurologic diseases not associated with the aforementioned conditions.

Senile plaques may be described [2] as small, spherical, thickened, argyrophil bodies scattered throughout the cerebral cortex (fig. 1 *a*). They are not uniform in structure, but consist of various components which are different in type and situation. Senile plaques vary in number and size, and their cellular elements may also vary, at times being numerous and at other times being scarce or totally absent from the plaque. The diameter of these plaques has been given as 10 to 150 microns.[2a]

Senile plaques generally are most numerous in the cortex of the frontal lobes and in the cornu ammonis.[3] In the studies of Sim-

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1. Blocq, F., and Marinesco, C.: Sur les lésions et la pathogénie de l'épilepsie dite essentielle, Semaine méd. **12**:445, 1892.

2. (*a*) Critchley, M.: The Nature and Significance of Senile Plaques, J. Neurol. & Psychopath. **10**:124-139 (Oct.) 1929. (*b*) Bouman, L.: Senile Plaques, Brain **57**:128-142 (June) 1934. (*c*) Biggart, J. H.: Pathology of the Nervous System, Baltimore, William Wood & Company, 1936.

3. (*a*) Tinel, J.: Les processus anatomo-pathologiques de la démence sénile, Rev. neurol. **2**:23-49 (July) 1924. (*b*) Simchowicz, T.: La maladie d'Alzheimer, et son rapport avec la démence sénile, Encéphale **1**:218-231 (March 25) 1914. (*c*) Simchowicz, T.: Sur la signification des plaques séniles et sur la formule sénile de l'écorce cérébrale, Rev. neurol. **1**:221-227 (Feb.) 1924. (*d*) Uyematsu, S.: On the Pathology of the Senile Psychosis: The Differential Diagnostic Significance of Redlich-Fischer's Miliary Plaques, J. Nerv. & Ment. Dis. **57**:1-25 (Jan.); 131-156 (Feb.); 237-260 (March) 1923. (*e*) Biggart.[2c]

chowicz,[3e] Uyematsu [3d] and Rothschild,[4] senile plaques usually were found to be most abundant in the regions of the cerebral cortex in which the most marked cellular degeneration and atrophy were discovered. Senile plaques have been observed in the basal ganglia and the cerebellum,[5] but Critchley [2a] stated that they are practically always confined to the cerebral cortex.

Within the cerebral cortex, the plaques appear chiefly in the deeper layers.[6] They are most abundant in the third cortical layer, and another favorite situation is the outer molecular zone of the gyrus dentatus. When the plaques are very numerous, they may occur in the other

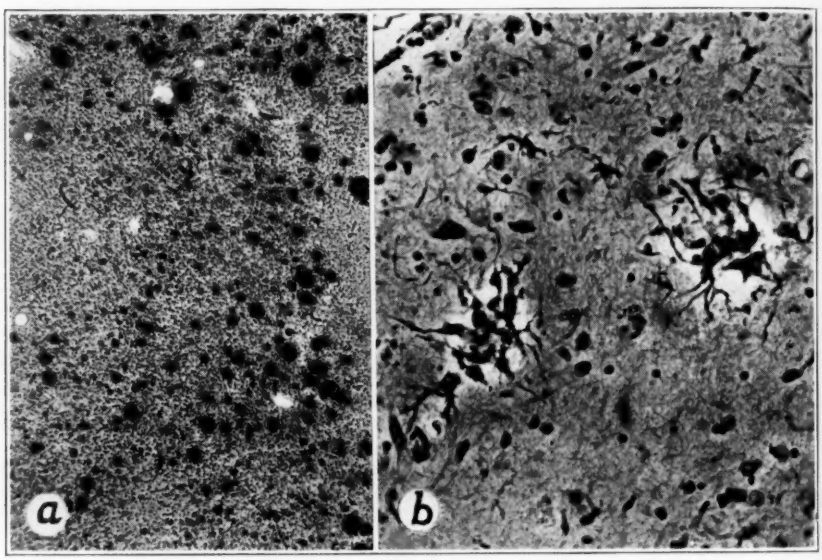


Fig. 1.—(*a*) Senile plaques scattered throughout the cerebral cortex (Orlandi's method; × 20); (*b*) two plaques consisting mainly of hypertrophied microglia cells which are clumped together (del Río Hortega's method; × 275).

cortical laminas, as well as in the immediately subjacent white matter. When the cerebellum is the seat of formation of plaques, the molecular layer is the structure usually involved, although plaques occasionally may be seen near the Purkinje cell layer.[6]

Critchley [2a] expressed the opinion that there has never been a satisfactory explanation of the almost exclusive selection of the cerebral

4. Rothschild, D.: Pathologic Changes in Senile Psychoses and Their Psychobiologic Significance, Am. J. Psychiat. **93**:757-788 (Jan.) 1937.

5. Ferraro, A.: The Origin and Formation of Senile Plaques, Arch. Neurol. & Psychiat. **25**:1042-1062 (May) 1931. Uyematsu.[3d]

6. Critchley.[2a] Uyematsu.[3d]

cortex as the seat of formation of plaques. He said that Löwenberg suggested two possible hypotheses: (1) that the predilection for formation of plaques in the cerebral cortex depended on the presence of capillary fibrosis in the senile cortex, or (2) that some peculiarity in the cortical reticulum favored formation of plaques.

## MATERIAL AND METHODS

The purpose of this investigation has been to study the origin and formation of senile plaques, independently of their distribution and of any attempt at clinicopathologic correlation. In the course of this study, 100 brains containing senile plaques were studied microscopically. This material had been obtained at necropsy from January 1918 to June 1939. The technic employed in this histologic study was that outlined by Kernohan.[7] In addition to routine staining with hematoxylin and eosin and with cresyl violet, various impregnation methods were used. Del Río Hortega's silver carbonate method was used for the study of microglia and oligodendroglia. Cajal's gold chloride and mercury bichloride method was used for study of astrocytes. The axis-cylinders, neurofibrils and nerve cells were studied with the silver impregnation methods of Bielschowsky, of Orlandi and of Bodian, the last two methods being used particularly.

## GENERAL HISTOLOGIC CONSIDERATIONS

Although it may be impracticable to attempt to divide senile plaques into different types, since all types probably have fundamentally the same mechanism of formation, not all these plaques look alike. This variation in appearance is referable to the fact that structure of the plaques depends on the intensity of the degenerative process which was operative and on the extent of reaction of the cellular elements.

With the hematoxylin and eosin stain many senile plaques appeared merely as round, unformed deposits which had taken the eosin stain somewhat more intensely than the surrounding tissue. The various aspects of senile plaques may be demonstrated best by the use of the silver impregnation methods. When these methods were employed, many of the plaques were seen to consist of a nuclear central mass, surrounded by a clear zone or halo, which in turn was surrounded by a darkly staining corona, or annular zone (the outer, or peripheral ring). The central mass either appeared to be homogeneous or contained very fine or coarse granules, which varied in amount. The corona was seen to consist of a meshwork of fibrillary material or of a precipitate of a dense granular substance. That fragmented neurites were the principal constituents of the annular meshwork could be demonstrated with Orlandi's method of impregnation. The cellular elements of senile plaques will be considered later.

7. Kernohan, J. W.: Preparation of Neurologic Material for Histologic Study, Am. J. Clin. Path. **4**:410-425 (Sept.) 1934.

Many plaques were diffuse, without a central mass or a ringlike arrangement of constituent elements. These plaques consisted of argyrophil clumps or fibrillar masses and, often, a varying amount of cellular elements. Some plaques were very cellular, some were extremely fibrillar and others consisted merely of granular debris. Some of the larger plaques undoubtedly had been formed by a fusion of small ones, since two or three small plaques often could be seen which were in the process of merging with each other. The earliest (smallest) type of plaque observed consisted of a disintegrating nerve cell or of a homogeneous mass around which were arranged a few argyrophil clumps (Orlandi and Bodian methods), or of a finely granular, argyrophil precipitate with a few microglia cells which were beginning to congregate around it (del Río Hortega method). The so-called perivascular plaques will be considered later.

*Microglia.*—Of all the cellular elements observed within senile plaques, microglia cells were most frequently encountered. Usually, proliferation of microglia in and around the plaque occurred. Only rarely did any microglia cell in the plaque or at its periphery appear to be normal in size and shape; usually they had undergone pathologic change. These microglia cells commonly were markedly hypertrophied, the cytoplasm being greatly increased in volume. Sometimes the processes appeared to be shortened and tuberous. A common observation was hypertrophied microglia cells, varying in number and often tending to be arranged in a roughly radial manner, clumped around a homogeneous or granular central mass. At times the central mass consisted of microglia cells, some of which contained dark granules. Another common observation was several hypertrophied microglia cells clumped together to form a small plaque (fig. 1 *b*). (Sometimes a few oligodendroglia cells were included in such a cluster.) Occasionally, a large swollen, solitary microglia cell situated in a granular, argyrophil precipitate was the only cellular constituent of the plaque. Even after impregnation with del Río Hortega's method some of the largest plaques appeared as structureless, granular portions of argyrophil precipitate. Sometimes hypertrophied microglia cells were seen which were not in proximity to a plaque.

Many of the hypertrophied microglia cells, in a plaque or at its periphery, had yellow cytoplasm containing dark, round granules. Sometimes these argyrophil granules themselves had a faintly yellow tint. (Del Río Hortega [8] stated that in microglia cells laden with fat or iron or both there are also found amorphous argyrophil granules representing intermediate stages in the elaboration of the materials.) The cytoplasm of the body of the cell as well as of the processes sometimes

8. del Río Hortega, P.: Microglia, in Penfield, W.,[16] pp. 483-534.

exhibited vacuolation. In rare instances typical gitter cells were found within the plaque or at its periphery. Apparently, most microglia cells within a plaque disintegrate before they reach the typical roundness of gitter cells. At times the cytoplasm of these microglia cells was rather diffusely granular and the processes were granular and fragmented, the whole cell apparently finally undergoing disintegration.

*Oligodendroglia.*—Oligodendroglia cells often were seen within or at the periphery of a plaque. In such a situation they were not numerous, usually numbering from one to three cells. Although many of them seemed to be normal, they often appeared to be undergoing degenerative changes. Sometimes evidence of satellitosis was found in the region of a plaque.

Occasionally the cytoplasm of degenerating oligodendroglia cells appeared to be swollen and the nucleus relatively normal, but usually the cytoplasm was swollen and finely granular and the nucleus had undergone pyknosis. Often all that could be discerned was the small, shrunken, hyperchromatic, oligodendroglial nucleus without surrounding cytoplasm, the cell membrane having disintegrated and disappeared. Several of these pyknotic nuclei often were seen within a plaque. Sometimes these nuclei appeared so distorted that it was difficult to identify them.

*Astrocytes.*—Astrocytes were generally somewhat increased around senile plaques, and there seemed to be a definite tendency for these cells to surround the plaques and to undergo changes of a progressive type (hypertrophy).

At times astrocytes seemed to be encapsulating the plaque with their processes; at other times they sent their processes into the plaque. Occasionally, the process projecting toward, into or across a plaque was undergoing degenerative change (fragmentation). Clasmatodendrosis of one or more of the astrocytes at the periphery of a plaque occasionally was observed, as was the occurrence of a hypertrophied or degenerated astrocyte within a plaque.

*Neurons.*—Senile plaques usually are associated with diffuse changes in the nerve cells,[9] which present some degree of atrophy and an accumulation of lipoid pigment, so that their basal portions are filled to a greater or lesser degree by yellow lipoid material. Lipoid pigmentation of nerve cells, according to Biggart,[2e] is a constant accompaniment of old age. Lipoid is present in the form of granules of lipofuscin, which

9. (*a*) Freeman, W.: Neuropathology: The Anatomical Foundation of Nervous Diseases, Philadelphia, W. B. Saunders Company, 1933. (*b*) Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934. (*c*) Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933. (*d*) Critchley.[2a] (*e*) Biggart.[2e]

appears as brown granules. Accumulation of this substance gradually increases with the approach of senility. In old age few cells remain unaffected; when senile plaques are extremely numerous (as in senile dementia) atrophy and pigmentation of the nerve cells are always marked. In the majority of cases of the latter type a diffuse reduction in the number of neurons occurs. Often the nerve cells show a granular degenerative change.

When the methods of impregnation of Orlandi, of Bodian and of Bielschowsky were used, discovery of a degenerating nerve cell within a plaque was common; sometimes it was situated in the center of the

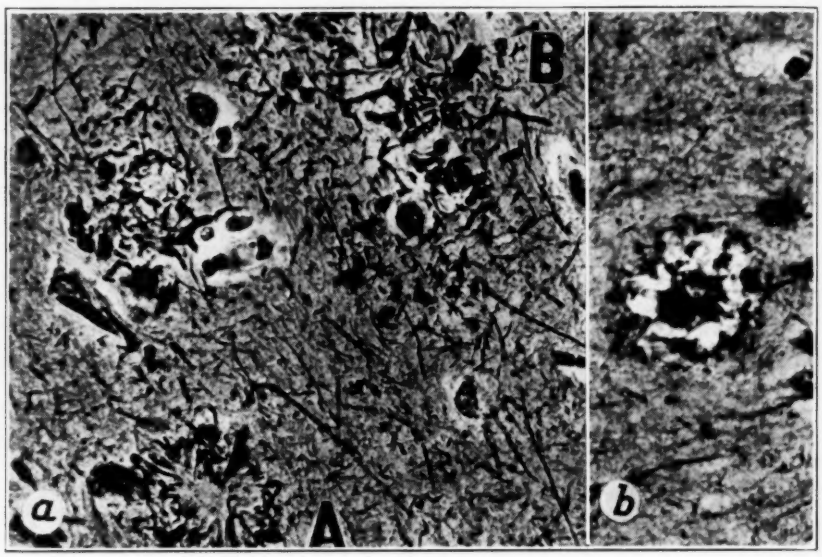


Fig. 2.—(*a*) Three senile plaques are seen: Plaque *A* exhibits the "sunburst" effect, the thickened neurites, bulbs and clubs; plaque *B* consists of remnants of nerve cells, neurofibrils and neurites; a pyramidal cell can be seen to be undergoing Alzheimer's change (Bodian's method; × 400). (*b*) Senile plaque showing, roughly, a central cellular body, a relatively clear halo and a peripheral annular zone, or corona (Orlandi's method; × 500). The central body consists of a nerve cell which is undergoing degenerative and disintegrative change.

plaque, at other times more peripherally. Sometimes the nucleus and nucleolus were the only parts of the nerve cell that could be discerned. Many plaques consisted of a homogeneous or slightly granular center with a "sunburst" of clubs leaving the plaque (fig. 2*a*). Yellow pigment often was observed in the center of a plaque and also in nerve cells nearby. Sometimes a shriveled nerve cell and fragmented neurites giving rise to a plaque could be seen.

Plaques in the process of formation consisted of a nerve cell surrounded by a moderate number of dark argyrophil granules. In such plaques, it could often be seen that the nerve cell was undergoing disintegration; the cell appeared to be swollen and granular or had lost its limiting membrane, its cytoplasm had become spread out irregularly and a dark granular precipitate had begun to form (fig. 2 *b*).

In a section stained with hematoxylin and eosin, a Purkinje cell was observed in the process of giving rise to a plaque. The whole cell appeared to be somewhat homogeneous, and although the nucleus and cytoplasm could be seen plainly, they did not accept the stain with that degree of contrast and distinctness which is usually seen. The Purkinje cell was surrounded and partly covered by more or less of a meshwork which was denser than the rest of the tissue. The neighboring Purkinje cells were normal in appearance; however, in some sections an occasional "torpedo" (a fusiform swelling of a process of a Purkinje cell) was encountered.

*Neurites.*—When impregnation of the axis-cylinders and neurofibrils with silver was employed, the senile plaque appeared as a meshwork or as a mass of intertwined argyrophil nerve fibers (fig. 2 *a*), which often contained degenerating nerve cells. The neurites seen within a plaque or just outside the periphery were fragmented. They were deeply stained and thicker than normal. Some of the fragments were granular; others were swollen, and many of these had bulbous ends (fig. 2 *a*). It was seen that some of the neurites entered the plaque and ended, within the plaque, in a bulbous end or club, whereas others emerged radially from the plaque and ended in bulbs or clubs which were, in this instance, arranged at the periphery of the plaque (sometimes in a "sunburst" effect, as seen in figure 2 *a*). Many of the nearby neurites ended in bulbs outside the plaque. Some of the longer neurites passed around the plaque and circumvented it, as if the enlarging plaque had gently pushed them aside, whereas others passed directly through the plaque. Sometimes clubs could be seen emerging from very early plaques. The bulbs and clubs occurred in various sizes. At times a plaque consisted of a granular mass of fragmented neurites without bulbs. Some neurites were observed to end in tiny, fibrillar, oval rings ("eyes"). Sometimes early plaques were observed which consisted merely of fragmented neurites (many having clubs) tangled up into a small mass.

*Alzheimer's Neurofibrillary Alteration.*—Alzheimer's intracellular neurofibrillary change was observed in approximately 75 per cent of the cases in which senile plaques were markedly numerous, in 50 per cent of the cases in which plaques were moderately numerous and in 10 per cent of the cases in which plaques were few.

Although some cells in the process of undergoing Alzheimer's alteration were seen within a plaque, usually they were situated just outside the periphery of the plaque (fig. 2 *a*), the reason for this being that these nerve cells generally disintegrate before becoming part of the plaque. In the peripheral situation, remnants of the cell, as it disintegrates, become part of the plaque and serve to increase the size of the plaque. Alzheimer's change consists of thickening and fusing of the intracellular neurofibrils, which are darker than normal and which tend to curl up, finally appearing as a tangled skein or whorl. This leads finally to disappearance of both cell body and nucleus, so that the curled or tangled neurofibrils are the only remnants of the nerve cell (fig. 3 *a*).

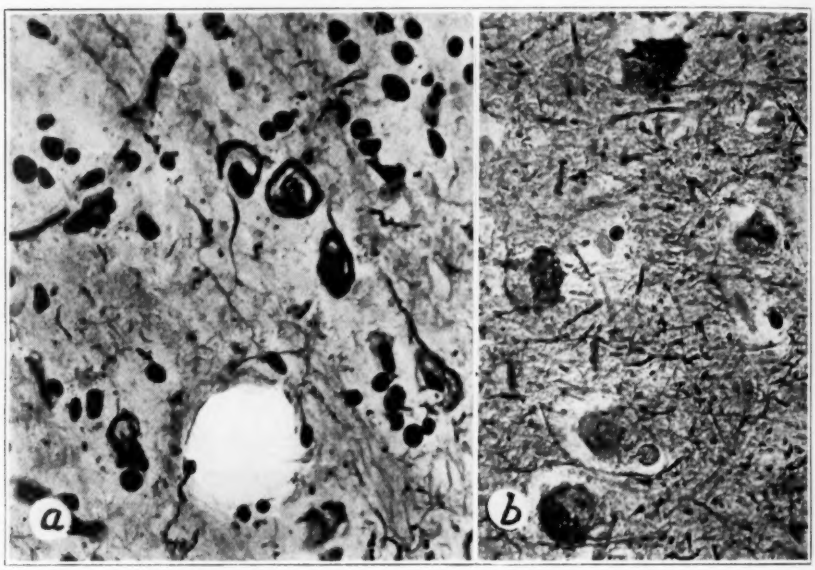


Fig. 3.—(*a*) Alzheimer's neurofibrillary alteration, with whorls and tangles; the membranes of the cells no longer can be seen (silver impregnation method; × 300). (*b*) Alzheimer's neurofibrillary alteration (Bodian's method; × 400). Several nerve cells showing this change can be seen. The dark, tangled neurofibrils have pushed the pale nucleus to one side of the cell. It can be readily seen that the bursting of any one of these cells would result in formation of a small, early senile plaque.

These remnants often were observed within a plaque (fig. 2 *a*); sometimes they composed the greater part. Huge confluent plaques containing many of these distorted, tortuous, fragmented remnants and many cells undergoing Alzheimer's change were observed. In a few instances Alzheimer's change was seen in a nerve cell which formed the center, and apparently the beginning, of an early plaque; sometimes free neurofibrillar remnants were seen in such plaques.

In the course of this study, various stages in Alzheimer's alteration were observed. The earliest stage seen was that in which the cytoplasm of the nerve cells contained dark, tangled filaments and in which the nucleus had been pushed to one side of the cell (fig. 3 *b*). Sometimes, instead of a tangle of filaments, a dark, more or less round mass was seen. Often pyramidal cells were observed in which there was a marked thickening of the neurofibrils along one or two sides of the triangular cells (fig. 2 *a*), between the membrane of the cell and the nucleus. At other times the neurofibrils were irregularly thickened throughout the cells. A few instances were observed in which a "cell cadaver," so to speak, was all that remained of the cell and in which the thickened neurofibrillar remnants apparently were in the process of giving rise to an early plaque. Some nerve cells contained dark granular material.

According to Bielschowsky,[10] the most common situation of the Alzheimer cell change is the frontal lobe, the cornu ammonis and the gyrus hippocampi. Marinesco and Minéa [11] found the regional distribution of the older plaques to be the same as that of the Alzheimer alteration. In brains in which few cells had undergone the neurofibrillary alterations of Alzheimer, Bouman [2b] also observed only simple or early plaques. In his cases of senile dementia he was always able to find cells in the cerebral cortex which showed this change, although in some he had to look carefully for them. According to Lhermitte and Cuel,[12] the number of Alzheimer changes which will be observed is, generally speaking, proportional to the number of plaques present. In Uyematsu's [3d] cases the number of cells exhibiting the Alzheimer change and the number of senile plaques were not always parallel. In the course of this study it was necessary to look carefully for the Alzheimer change, since this lesion does not become impregnated as readily as the plaque; moreover, if there was the slightest imperfection in the technic of the impregnation it was not seen.

### HISTOCHEMICAL STUDIES

Sections from 6 brains in which senile plaques were numerous were stained for amyloid, mucin, fat and glycogen. Congo red was used for amyloid, Mayer's mucicarmine technic for mucin, sudan III for fat and Best's technic for glycogen. The results of these histochemical studies were much too indefinite and inconsistent to warrant any conclusions.

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10. Bielschowsky, M.: Histopathology of Nerve Cell, in Penfield, W.,[16] vol. 1, pp. 147-188.

11. Marinesco, G., and Minéa, J.: Etudes sur la constitution des plaques dites séniles (Deuxième note), Compt. rend. Soc. de biol. **70**:669-671, 1911; Nature des plaques séniles (Troisième note), ibid. **70**:882-883, 1911.

12. Lhermitte, J., and Cuel, J.: Sur l'anatomie pathologique de la maladie d'Alzheimer, Encéphale **19**:237-241 (April) 1924.

PERIVASCULAR PLAQUES

Apparently, no correlation exists between atherosclerosis of the cerebral blood vessels and the formation of senile plaques; however, brains containing plaques often may exhibit some degree of atherosclerosis of the blood vessels. The possibility that senile plaques may be the result of nutritional disturbances occurring in the immediate vicinity of the blood vessels has been taken into consideration by various authors.[13] However, as Ferraro [5] said, during discussion on his paper: "The point to be considered mainly is whether the nutritional changes influence primarily the nerve cells, the neuroglia cells or the fundamental interstitial substance." That perivascular genesis has a part in the development of senile plaques has been insisted on by Uyematsu,[3d] Bouman [2b] and Critchley.[2a]

Sometimes plaques are situated adjacent to or in close proximity to blood vessels, but usually there is no such relationship. In this study, a few small plaques were seen the center of which was occupied by a small, patent blood vessel which had been cut transversely; most of these vessels had normal walls, but in rare instances the walls showed hyaline change. Occasionally, a small blood vessel, cut longitudinally, was seen to pass through a plaque. An occasional plaque was observed in the fork formed by a small, branching blood vessel. In rare instances the argyrophil clump (plaque in a very early stage of development) situated just at the edge of a transversely cut blood vessel, as described by Bouman (referred to by Critchley [2a]), was noted.

That a certain proportion of senile plaques should be situated in the immediate neighborhood of small blood vessels is to be expected, especially if the work of Pfeifer [14] is borne in mind. Pfeifer demonstrated of what an intricate network of abundant, relatively closely approximated blood vessels the vascular architecture of the brain really consists. Bouman's argyrophil clump conceivably could be a plaque in an early phase of development springing from a degenerated nerve cell which, by chance, was situated adjacent to a small blood vessel. Those plaques which surround a blood vessel in a concentric manner cannot be explained satisfactorily by the element of chance. In such instances the plaque is composed of fibrils of indefinite character and of a fine granular detritus rather than of cellular elements. This observation is pertinent, for in many cases it is difficult to distinguish such a plaque

13. Bonfiglio, F.: L'anatomia patologica delle psicosi dell' età senile, Riv. sper. di freniat. **45**:219-250 (Jan.) 1922. Grünthal, E.: Klinisch-anatomisch vergleichende Untersuchungen über den Greisenblödsinn, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:763-818, 1927.

14. Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

from a rather characteristic artefact seen in some improperly silver-impregnated sections, in which a fine granular precipitate is seen surrounding many small blood vessels (the section in figure 3 of Uyematsu's article resembles such an artefact). Uyematsu concluded that the concentrically arranged perivascular plaque was an abnormal reaction of the reticulum to degenerating blood vessels; yet he wrote that only some of the vessels in these plaques were notably altered, whereas others were apparently normal. Is the latter type of so-called perivascular plaque a true senile plaque, comparable to plaques occurring independently of blood vessels, or is it merely the result of an increased precipitation of silver around these blood vessels for some reason totally divorced from formation of plaques?

## COMMENT

The observations with which the preceding sections of the paper have dealt have been described in an episodic manner, for the reason that there is no one method for the staining or impregnation of tissues which will bring into relief all the various elements which compose the substance of the brain. It must be borne in mind that the formation of senile plaques really consists of a composite picture of the various episodes. At best, this picture is static as compared with dynamic pathologic processes which take part, in the living person, in the formation of these plaques. Histologic methods being what they are, missing links often must be supplied by logical inference.

There is definite evidence that senile plaques do arise primarily from degenerating nerve cells, and the results of this study would seem to indicate that the great majority (if not all) of the plaques have such an origin. Identifiable degenerating nerve cells often are seen in the center of plaques in an early stage of development. Cells situated at the periphery of a plaque often are observed to be undergoing changes of the same morphologic nature as that of the plaque. Many early plaques bear a striking resemblance to "exploded" nerve cells. It can easily be visualized that the bursting of a nerve cell which is undergoing Alzheimer's neurofibrillary change would result in formation of a senile plaque. Observations made in the course of this study seem to indicate that a great proportion of senile plaques arise from Alzheimer's neurofibrillary alteration of nerve cells. The remnants of these thickened, whorled fibrils are commonly observed in senile plaques in preparations which have been properly impregnated with silver. Perhaps the excess of lipoid pigment in the nerve cells and the granular type of degeneration of nerve cells seen in these cases also could initiate the pathologic process which ends in the formation of a plaque. The metabolic and chemical processes which initiate degeneration of the nerve cells are as

yet obscure, and much additional knowledge will be necessary before even a guess as to their nature can be hazarded.

Critchley wrote: "It was pointed out, however, that the occasional finding of plaques in the molecular layers of the cortex and in the white matter is evidence against their neuronic origin." This led Fuller [15] to contend that plaques did not have an origin in degenerating nerve cells. Such a statement is misleading; neurons do occur in the first (molecular) layer of the cortex,[9b] although in such a situation they are small and few, whereas they are larger and much more numerous in the deeper layers (for example, the pyramidal cell layer) of the cortex. It also must be pointed out that senile plaques occurring in the first cortical layer are few (a fact of which Critchley must have been aware since in the quotation previously cited he used the phrase "the occasional finding"). As to the occasional observation of senile plaques in the white matter, it must be remembered that "gray matter" and "white matter," as the words imply, are intrinsically gross anatomic divisions. Microscopically there is no perfectly sharp line of demarcation between these portions: They tend gradually to blend one into the other. Large nerve cells are to be found in the so-called white matter beneath the cerebral convolutions; consequently, nerve cells are often seen to be situated deeply, a long distance from the pial border of the cortex, in a scattered manner among the myelinated axis-cylinders ("stray sheep," as it were). In this study, only a few plaques were observed in the white matter; these were always situated very near the zone in which gray and white matter blend into one another, and a neuron invariably was situated nearby, a fact which demonstrated that the plaques were not in a region devoid of nerve cells.

According to Biggart, the earliest appreciable histologic change in damaged axis-cylinders is some degree of swelling, with an increased affinity for silver. The swollen axis-cylinders become tortuous and nodular and they gradually fragment. The fragments occasionally exhibit spiral and bulbous formations, and sometimes appear to be granular. When nerve fibers regenerate, many fibrils exhibit end bulbs, and some are covered with terminal ringlets and loops. These phenomena of regeneration appear with the degeneration, and it is hard to decide when one phase ends and the other begins. In the central nervous system, in an attempt to regenerate, the nerve fibers form small bulblike endings from which thin fibrils emanate. However, these represent only abortive attempts at regeneration; they produce no results and are not stable. As Bouman wrote, "There is never more than an indication of this process [regeneration], and the newly formed material seems

15. Fuller, S. C.: A Study of the Miliary Plaques Found in Brains of the Aged, Am. J. Insan. **68**:147-219 (Oct.) 1911.

to have only a short life." Biggart stated that in the central nervous system no successful repair of injured axis-cylinders occurs, although slight proliferation of neurofibrils may be found. Thus, it would seem logical to assume that the swollen and fragmented neurites and the bulbs and clubs found in senile plaques are part of a process of degeneration and that if any phenomena of regeneration are present, they are relatively scarce and of negligible importance so far as the formation of senile plaques is concerned. Many of the small bulbs may be *boutons terminaux* on the ends of dendritic remnants.

The question arises whether the changes observed in the microglia cells are the initial cause of formation of the plaques or whether these microglial alterations are secondary phenomena occurring after the necrobiotic foci have already begun to form. It might be concluded on the basis of this study that the interstitial reaction is dependent on destruction of parenchyma, in the particular region under consideration, as elsewhere in the human body, and in this particular process, as in other pathologic processes affecting the brain. The physiologic role of the microglia cells (cerebral histiocytes) is active intervention, in all inflammatory and necrotizing processes of nerve tissue, to eliminate substances resulting from metabolism or neuronal breakdown by the phagocytosis of cellular remnants. Why should not small necrobiotic foci (plaques) attract and induce the intervention of microglia? Proliferation, clumping and increase in number of the microglia cells in and around senile plaques certainly constitute evidence that these cells in such a situation are attempting to carry out their physiologic function. Although the microglia cells can be seen to contain granular and lipoid inclusions, which apparently are engulfed debris, they do not succeed very well in pursuing their physiologic role, and themselves undergo degenerative changes and disintegration in the process. Thus, microglia cells contribute to the formation of senile plaques by enlarging the size of the plaques, by means of both active intervention and disintegration.

There is evidence that the astrocytes, at least at times, attempt to encapsulate the plaques. There is no good evidence that plaques ever arise primarily as the result of degeneration of astrocytes.

The oligodendroglia cells which happen to be situated near the site of a plaque which is in an early stage of development participate in increasing the size of the plaque when they become included in the enlarging necrobiotic process. Some of these cells are undergoing degenerative change. What initiates such a degeneration of the oligodendroglia, as previously described, can only be surmised. The same change may be observed in oligodendroglia cells which are not situated in proximity to a plaque. There seems to be no real increase in the number of oligodendroglia cells in a plaque or in the immediate vicinity of a plaque. It is a well established fact that these cells readily undergo

regressive changes; they are observed to be swollen in the brains of persons who had coma or delirium at the time of death. Penfield [16] expressed the belief that acute swelling of the oligodendroglia is the most sensitive of all pathologic changes in the brain and that some degree of this change is to be found in practically all brains observed at necropsy. For the aforementioned reasons, extreme caution must be used in interpretation of the oligodendroglial changes observed in association with senile plaques.

The fact that oligodendroglia are seen in senile plaques in no way indicates that these cells give rise to the plaques. In the cortex these cells usually are seen in close association with nerve cells, and the phenomenon of satellitosis is present to some degree in brains containing senile plaques.

The fact that Hiroisi and Lee [17] were able to stain senile plaques and to obtain positive reactions for the presence of mucin does not indicate that plaques arise as the result of mucoid degeneration of oligodendroglia. Although the swelling of oligodendroglia cells appears to be most often referable to some form of hydropic change in the cytoplasm, occasionally the cell yields a positive reaction for mucin. It is known that some plaques contain oligodendroglia cells, some of which in turn contain a substance which gives a positive stain for mucin. Beyond such a statement it is not possible to go.

## CONCLUSIONS

The great majority, if not all, of senile plaques arise primarily from nerve cells which have undergone degeneration; in a great proportion of these cells the degeneration consists of Alzheimer's neurofibrillary change. The resulting necrobiotic focus (consisting of remnants of nerve cells, axons, dendrites and neurofibrils) attracts the microglia cells, which, while attempting to function in their physiologic role, may become a part of the plaque. The oligodendroglia cells most probably become involved in the plaque by mere coincidence. There is evidence that the astrocytes, at least at times, attempt glial repair of the plaque.

Methods of research are, as yet, not adequate enough to provide an explanation of the complex biochemical processes which cause degeneration of the nerve cells, and hence initiate formation of the senile plaque.

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16. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 423-479.

17. Hiroisi, S., and Lee, C. C.: Origin of Senile Plaques, Arch. Neurol. & Psychiat. **35**:827-838 (April) 1936.

# OCCLUSION OF THE SUPERIOR CEREBELLAR ARTERY

## REPORT OF A CASE WITH NECROPSY

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AND
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Although the syndrome of the superior cerebellar artery is well recognized clinically, only eight reports appear in the literature,[1] representing a total of 22 cases since the first description by Mills,[1a] in 1908. There is a particular paucity of cases in which this vessel has been involved with reasonable selectivity and which offer adequate opportunity for clinical observations with subsequent postmortem confirmation. On this account there has arisen considerable speculation regarding certain anatomic and functional problems, and the present case is reported with the hope of contributing relevant data.

Of incidental interest is the fact that this is the first recorded case of occlusion of the superior cerebellar artery occurring as the result of an embolus in a patient with subacute bacterial endocarditis. It should also be noted that death occurred about two months after the apparent onset of the intracranial complication, an interval which made possible the

From the Departments of Neurology, George Washington University and Gallinger Municipal Hospital.

Read before the Section on Neurology and Psychiatry of the Medical Society of the District of Columbia, Oct. 3, 1940.

1. (*a*) Mills, C. K.: Hemianesthesia to Pain and Temperature and Loss of Emotional Expression on the Right Side with Ataxia of the Upper Limb on the Left, J. Nerv. & Ment. Dis. **35**:331, 1908. Spiller, W. G.: Remarks on the Central Representation of Sensation, ibid. **42**:399, 1915. (Pathologic report on Mills's case.) (*b*) Guillain, G.; Bertrand, I., and Péron, W.: Le syndrome de l'artère cérébelleuse supérieure, Rev. neurol. **2**:835, 1928. (*c*) Worster-Drought, C., and Allen, I. M.: Thrombosis of the Superior Cerebellar Artery, Lancet **2**: 1137, 1929. (*d*) Tchernysheff, A., and Grigorowsky, I.: Ueber die arterielle Versorgung des Kleinhirns, Arch. f. Psychiat. **92**:8, 1930. (*e*) Russel, C. K.: The Syndrome of the Brachium Conjunctivum and the Tractus Spinothalamicus, Arch. Neurol. & Psychiat. **25**:1003 (May) 1931. (*f*) Critchley, M., and Schuster, P.: Beiträge zur Anatomie und Pathologie der Arteria cerebello superior, Ztschr. f. d. ges. Neurol. u. Psychiat. **144**:681, 1933. (*g*) Davison, C.; Goodhart, S. P., and Savitsky, N.: The Syndrome of the Superior Cerebellar Artery and Its Branches, Arch. Neurol. & Psychiat. **33**:1143 (June) 1935. (Case 1 reported separately by Sandler, S. A.: J. Nerv. & Ment. Dis. **82**:263, 1935.) (*h*) Amyot, R.: Le syndrome de l'artère cérébelleuse supérieure, Union méd. du Canada **68**: 1067, 1939.

application of the Marchi method in preparing the microscopic sections. Earlier degenerative changes could thus be demonstrated, presenting an advantage over the Weigert preparations used in the cases which have been reported.

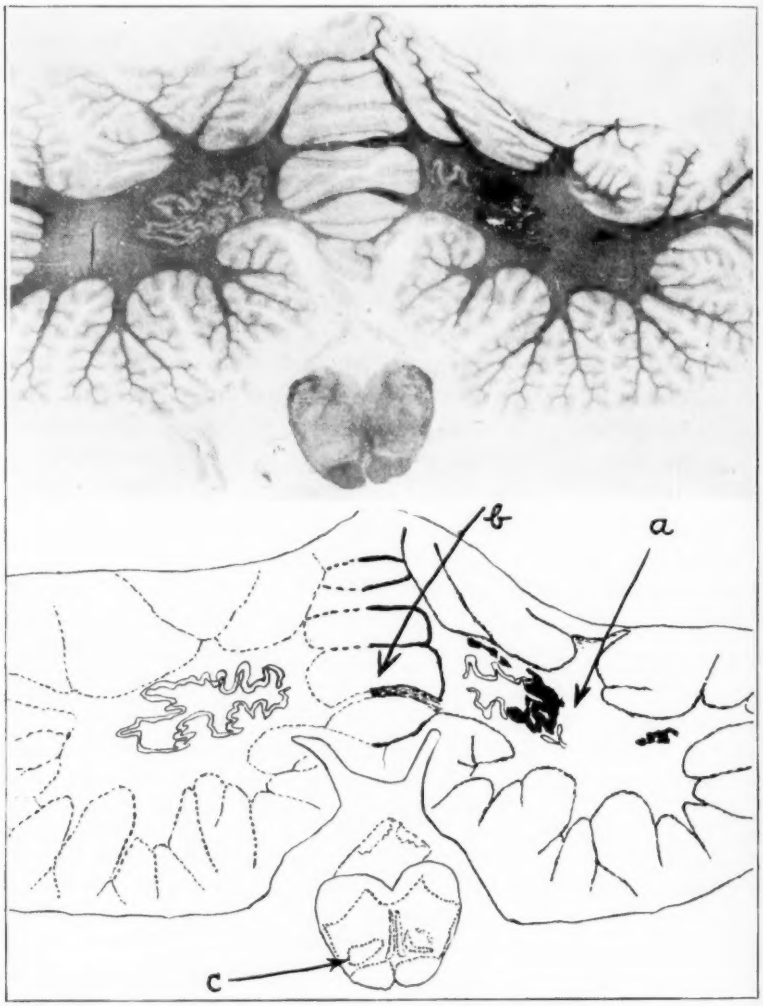


Fig. 1.—Section through the medulla at the level of the inferior olives. In this figure, *a* indicates infarction in the lateral half of the left dentate nucleus and degeneration in the white substance of the lobulus simplex and lobulus ansiformis $C_1$; *b*, degeneration in the lobulus $C_2$ vermalis, as far as the midline, and *c*, hypertrophic degeneration of the contralateral inferior olive.

## REPORT OF CASE

*History.*—J. G., a Negro aged 44, was admitted to the Gallinger Municipal Hospital on Nov. 27, 1939, in a confused state. The history was obtained from

his wife. He had had "rheumatism" for ten years and for the past four years had suffered pains in the joints of the legs which confined him to bed for two to three weeks from time to time. For the past six months he had been in bed almost constantly because of pains in the knees and ankles. At the time of

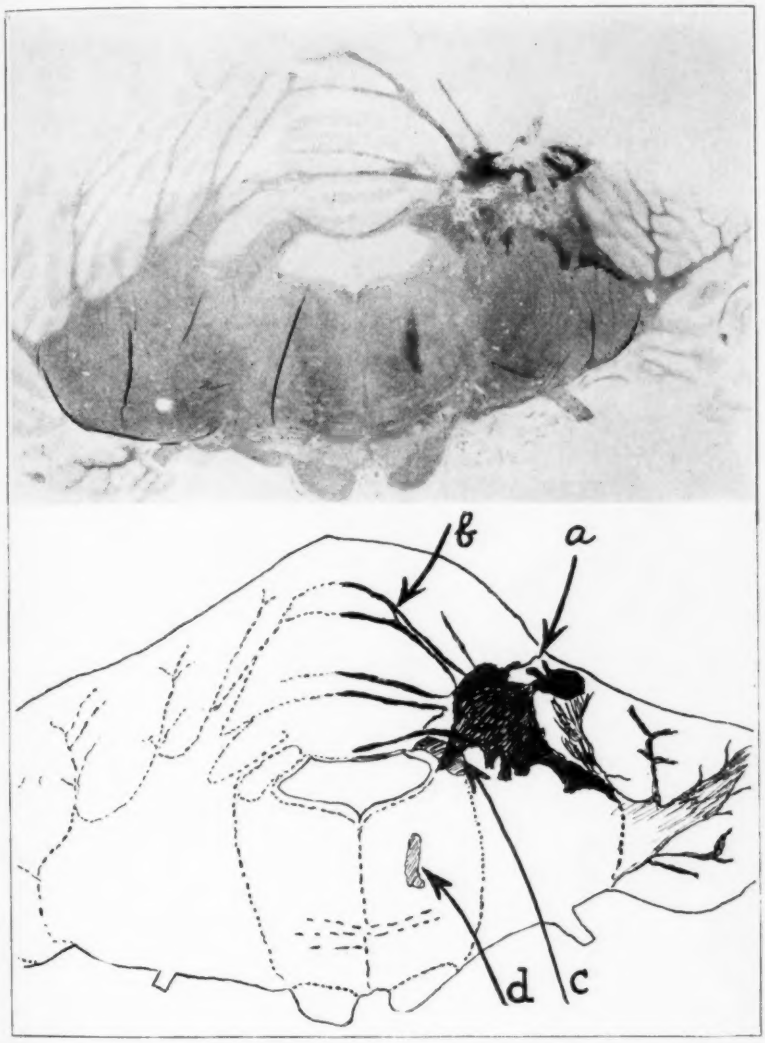


Fig. 2.—Section through the pons at the level of the eighth nerve. Here, *a* indicates infarction in the lobulus anterior and dorsal portions of the restiform body and brachium pontis, opposite the entrance of the eighth nerve; *b*, degeneration in the lobulus II vermalis, reaching just to the midline; *c*, infarction in the angle of the fourth ventricle, involving the brachium conjunctivum and Gowers' tract with degeneration in the brachium conjunctivum, and *d*, degeneration of the central tegmental fasciculus on the left side.

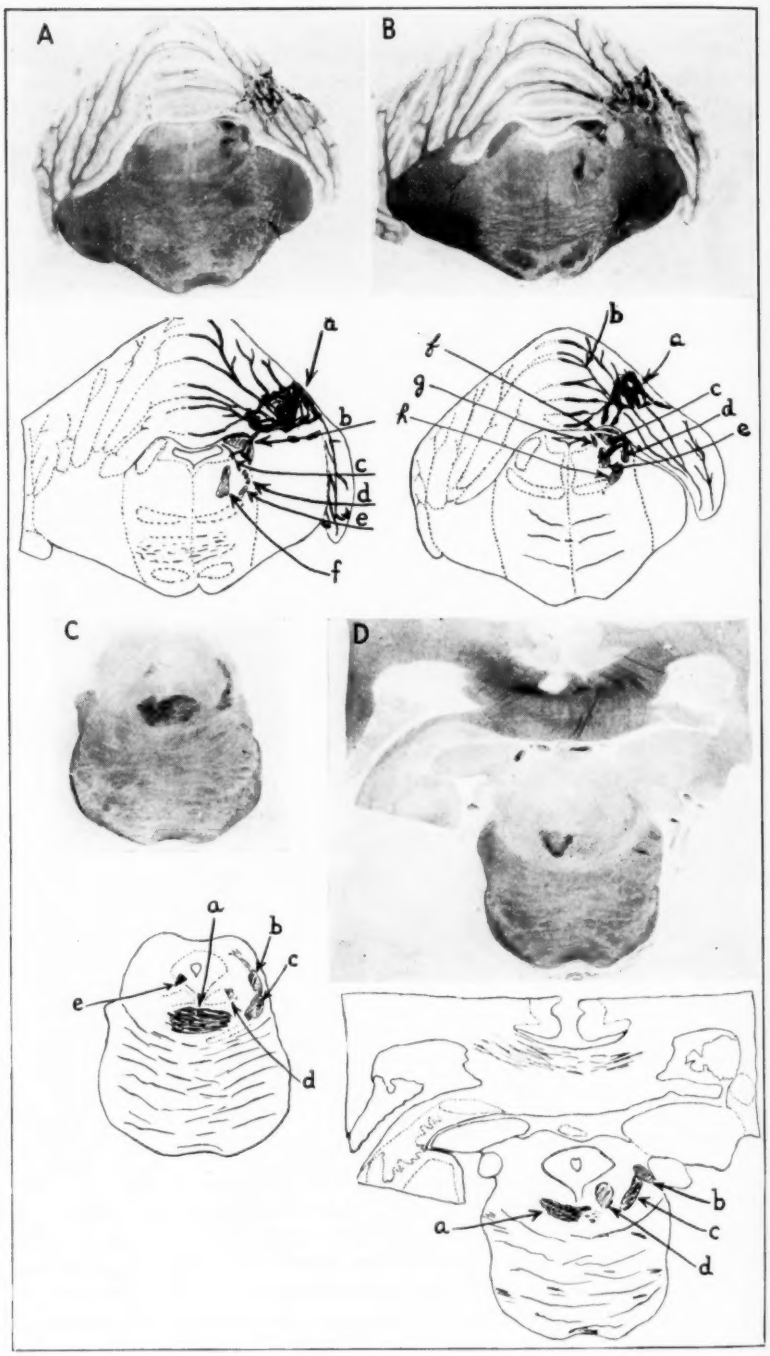


Figure 3

*(See legend on opposite page)*

admission he complained of numbness in both legs; the left leg felt hot and the right cold.

Information was meager as to the rest of his history. There was a vague story of a penile lesion five years previously, but the details were uncertain. For an indefinite period the patient had received injections in the hip, but none in the arm.

*Examination.*—On admission, the temperature was 101 F., the pulse rate 100 and the blood pressure 140 systolic and 50 diastolic. The patient appeared fairly well nourished; he was confused and dyspneic. The pupils were pinpoint and failed to react to light or in accommodation. Marked carotid pulsations were noted, and the "entire bed shook with each cardiac systole." The apical impulse was diffuse, reaching to the sixth interspace in the anterior axillary line. No thrills were noted. To and fro murmurs were heard over the aortic and mitral areas and were transmitted along the vessels of the neck, as well as toward the apex. The abdomen was flat; the liver was palpable, but the spleen was not felt. There was no ascites or edema.

The electrocardiogram showed left axis deviation and delayed auriculoventricular conduction (0.28 second).

A roentgenogram showed enlargement of the left ventricle but no dilatation of the aorta.

Petechiae were noted in the mucous membranes from time to time, and blood cultures yielded organisms on three occasions, on two of which nonhemolytic and on one hemolytic streptococci were reported.

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EXPLANATION OF FIGURE 3

Fig. 3.—*A*, section through the pons above the level of the seventh nerve. Here, *a* indicates infarction in the cerebellum, as previously noted; *b*, infarction extending into the pons, involving the brachium conjunctivum and Gowers' tract and, *c*, the mesencephalic root of the trigeminal nerve; *d*, degeneration in the lateral lemniscus, which appears grouped in bundles; *e*, degeneration in the spinothalamic tract, and *f*, degeneration in the central tegmental fasciculus.

*B*, section through the pons below the decussation of the brachium conjunctivum. (*a*) Infarction in the lobulus anterior; (*b*) degeneration in the lobulus IV vermalis, extending to the midline; (*c*) infarction in the pons, involving the brachium conjunctivum; (*d*) lateral lemniscus and (*e*) central tegmental fasciculus; (*f*) degeneration in Gowers' tract; (*g*) degeneration in the mesencephalic root of the trigeminal nerve, and (*h*) degeneration in the spinothalamic tract. The locus caeruleus and the median longitudinal fasciculus were uninvolved.

*C*, section through the inferior colliculi. Here, *a* indicates ascending degeneration, marking the decussation of the brachium conjunctivum; *b*, ascending degeneration in the lateral lemniscus, reaching toward the inferior colliculus; *c*, ascending degeneration in the spinothalamic tract; *d*, slight degeneration in the region of the central tegmental fasciculus, and *e*, area of darkening in the central gray matter, probably representing a small embolic focus independent of the main lesion. (At higher levels several small embolic foci are seen.)

*D*, section through the superior colliculi. Here, *a* indicates ascending degeneration in the crossed fibers of the brachium conjunctivum; *b*, degeneration in the lateral lemniscus; *c*, degeneration in the spinothalamic tract, and *d*, faint darkening in the central tegmental region. Incidental degeneration is noted in the splenium of the corpus callosum and in the pontile nuclei and transverse fibers.

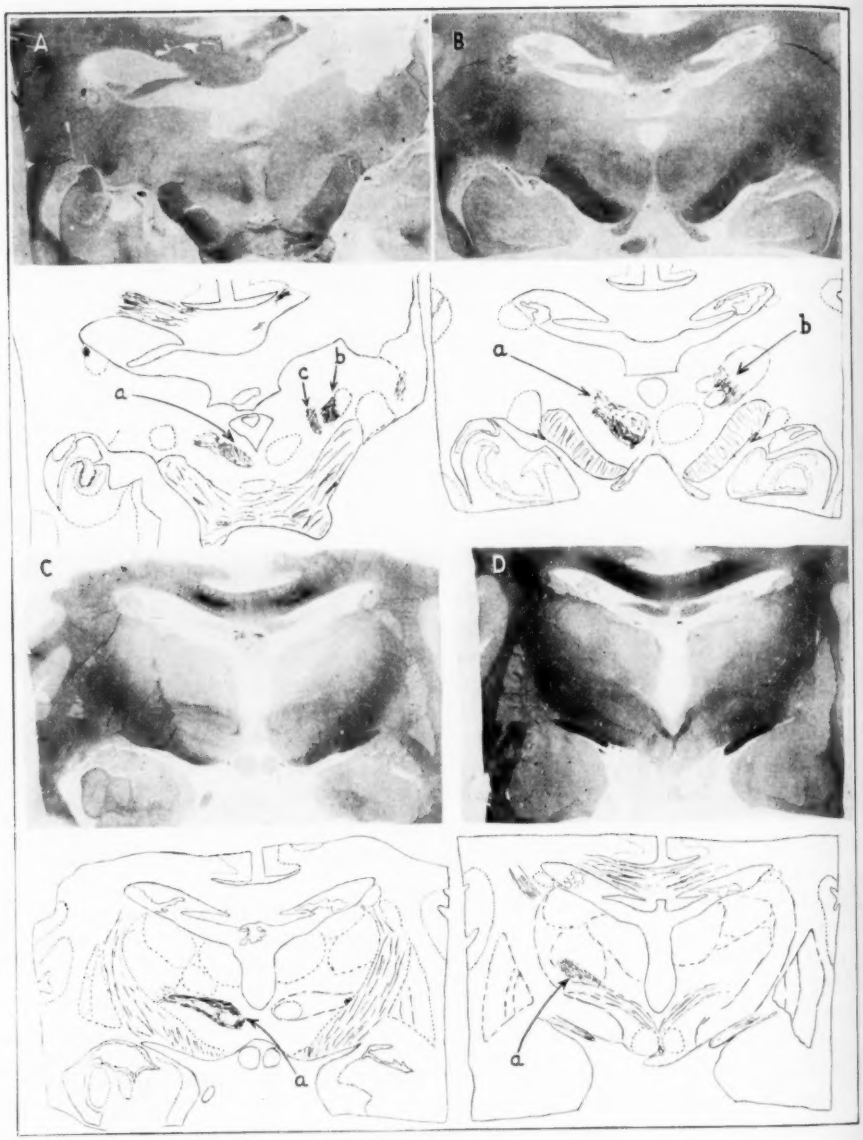


Figure 4

(See legend on opposite page)

The red cell count was 3,000,000, the hemoglobin concentration 50 per cent and the white cell count 20,000, of which 50 per cent were segmented polymorphonuclears, 22 per cent band forms, 21 per cent lymphocytes and 7 per cent monocytes.

Urinalysis revealed albumin, casts, occasional red blood cells and leukocytes.

The Kahn reaction of the blood was negative.

*Intracranial Complication.*—On December 4 it was noted that the patient had marked tremors of the left hand and arm, and neurologic examination gave the following results:

1. The pupils were unequal, the right being larger than the left. The left pupil was irregular and miotic and measured 1.5 mm. Both reacted sluggishly to light.

2. A Horner syndrome was present on the left, with ptosis of the left lid, enophthalmos, miosis of the left pupil and absence of sweating on the left side of the face.

3. No facial weakness was noted on voluntary motion. Slight amimia of the left side of the face appeared on smiling and marked paresis of the right side of the face on wincing.

4. Hearing was impaired bilaterally. A watch was not heard at all when held to the right ear and was heard at 2 inches (5 cm.) when held to the left ear. It was heard by normal control at 10 inches (25.4 cm.). The Weber test showed lateralization to the left; bone conduction was greater than air conduction.

5. Cerebellar signs were marked hypotonia on the left side, involving the upper and lower extremities, rebound phenomenon, intention tremor, dysmetria, asynergia and adiadokokinesis. Speech was thick and difficult to understand.

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EXPLANATION OF FIGURE 4

Fig. 4.—*A*, section through the red nucleus and diencephalon at the level of the pulvinar. (*a*) Degeneration in the red nucleus on the right side (the first way station in the pathway of the crossed brachium conjunctivum), with continuation toward the thalamus. Degeneration is seen outside the boundaries of the red nucleus. (*b*) Darkening at the inner aspect of the medial geniculate body on the left side, representing the upper limit of the ascending degeneration in the corresponding lateral lemniscus. (*c*) Continuation of the spinothalamic degeneration, spreading out toward the thalamus. Incidental foci are noted in the splenium of the corpus callosum, the body of the caudate nucleus, the basis pedunculi, the sublenticular portions of the internal capsule and the dentate fascia of the hippocampus.

*B*, section at the level of the third nucleus. (*a*) Degeneration in the red nucleus on the right side, with degeneration in the dentatothalamic projection beyond the borders of the red nucleus. (*b*) Degeneration in the posterolateral ventral nucleus of the thalamus on the left side, representing the upper limit of the ascending degeneration in the spinothalamic tract.

*C*, section through the mamillary bodies. (*a*) Degeneration in the red nucleus and region of the corpus subthalamicum on the right side, which may be followed laterally and upward toward the lateral ventral nucleus of the thalamus.

*D*, section through the mamillary bodies and mamillothalamic fasciculi. (*a*) Blackened areas in the lateral ventral nucleus of the thalamus on the right side, representing the upper limit of the ascending degeneration in the crossed brachium conjunctivum.

6. There were analgesia to temperature, pinprick and deep pressure pain over the right side of the body, including the face, and hypesthesia to light touch. Vibratory sensation was present on both sides; position sense was occasionally absent on the right.

7. Deep tendon reflexes were increased throughout, being more active on the right. A positive Hoffmann and an equivocal Babinski sign were elicited on the right. Abdominal and cremasteric reflexes were absent.

8. There were slight nuchal rigidity and a Kernig sign bilaterally.

*Examination of Spinal Fluid.*—The pressure was 160 mm. of water and rose to 320 mm. on jugular pressure, with a prompt fall to 140 mm. The Kahn reaction was negative. The cell count was 12 lymphocytes per cubic millimeter. The total protein measured 100 mg. per hundred cubic centimeters, the sugar 62 mg. and the chlorides 726 mg. The colloidal gold curve was 552111000.

*Course.*—On December 13 weakness of the left trapezius muscle was noted. On January 2 a gross, coarse tremor became evident, which was present while at rest and involved the entire left side of the body, including the face and lower jaw, and questionable myoclonic movements of the soft palate were noted. The tremor was rhythmic, with a rate of about 200, and appeared to be twice as fast as the pulse. On February 5 palsy of the left abducens nerve developed, and it was noted that the left pupil was now dilated. The visual fields and fundi remained normal. On February 12 irregular, gross tremor of the right hand was seen while at rest. The temperature curve spiked from 99 to 103 F. during the course of the illness, and on February 13 the patient died.

*Necropsy.*—The diagnosis of subacute bacterial endocarditis was confirmed by the presence of numerous firm, yellowish gray vegetations on all three cusps of the aortic valve and vegetations with aneurysm formation on the aortic cusp of the mitral valve. In addition, there were areas of infarction in the spleen, kidneys and right lung; numerous petechial hemorrhages, and an ulcer of the stomach, possibly of embolic origin.

The brain was firm and presented a normal appearance over the cerebral surfaces. On palpation the left cerebellar hemisphere appeared somewhat softened at the lateral margin of the anterior lobule. Removal of the arachnoid forming the cisterna pontis revealed the superior cerebellar arteries. The vessel on the left was yellowish, narrow, tortuous and nodular; it was completely occluded for about 2.5 cm. of its length, from its origin at the basilar artery to its visible termination.

After complete fixation, an area of brownish discoloration, measuring 2 by 1 cm., was seen on the superior surface of the left cerebellar hemisphere above the corpus dentatum, and the folia over this area appeared confluent.

Serial sections, prepared by the Marchi method,[2] revealed an area of infarction in the left cerebellar hemisphere, involving the lateral half of the dentate nucleus, and extending into the brachium conjunctivum and dorsolateral tegmentum of the pons. In addition, there were degeneration of neighboring fiber tracts deriving

2. The sections were prepared under the direction of Prof. Adolf Meyer, of the Henry Phipps Psychiatric Clinic.

their blood supply from the superior cerebellar artery and ascending degeneration of distant structures in the brain stem.

The classification of the cerebellar lobules used in this study is that of Riley,[3] as modified by Davison and his associates.[1g]

## COMMENT

*Anatomic Observations.*—An area of infarction is demonstrated, involving the left dentate nucleus, the lobulus anterior of the cerebellum, the brachium conjunctivum and Gowers' tract; a small portion of the restiform body and brachium pontis; the lateral lemniscus; the central tegmental fasciculus, and the lower part of the mesencephalic root of the trigeminal nerve. Degeneration resulting from vascular occlusion is noted in the left cerebellar hemisphere and includes the lobulus anterior, lobulus simplex and lobulus ansiformis $C_1$; the lobulus $C_2$ vermalis, lobulus II vermalis and lobulus IV vermalis on the left side as far as the midline, and, in the brain stem, the spinothalamic tract, in addition to the structures involved by infarction.

Ascending degeneration is traced along the left brachium conjunctivum, through its decussation, to the way stations in the red nucleus and the lateral ventral nucleus of the thalamus on the right side.

The left lateral lemniscus is followed upward through the brain stem to the inferior colliculus and the medial geniculate body of the same side.

Degeneration of the spinothalamic tract extends throughout the pons and midbrain and can be followed into the posterolateral ventral nucleus of the thalamus on the left side.

The mesencephalic root of the trigeminal nerve is involved by the infarct in the pons, and degeneration is followed for a short distance above the lesion. At the level of the inferior colliculi, and higher in the midbrain, no evidence of degeneration is seen. This observation lends support to the opinion, expressed by one of us,[4] that this tract in its upper portion is made up of incoming oculomotor sensory (kinesthetic) fibers.

Hypertrophic degeneration is noted in the inferior olive on the right side, corresponding to the involvement of the dentate nucleus on the left. No degeneration is seen in the central tegmental (thalamo-olivary) fasciculus on the right side, but on the left there is conspicuous degeneration of this tract, with no apparent change in the left inferior olive.

Infarction is seen involving Gowers' tract, and descending degeneration is noted to a slight extent.

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3. Riley, H. A.: The Lobules of the Mammalian Cerebellum and Cerebellar Nomenclature, Arch. Neurol. & Psychiat. **24**:227 (Aug.) 1930.

4. Freeman, W.: The Columnar Arrangement of the Primary Afferent Centers in the Brain-Stem of Man, J. Nerv. & Ment. Dis. **65**:378, 1927.

There is no descending degenerated tract that can be considered as sympathetic. Possibly such fibers are too thinly myelinated to be identified.

*Clinicopathologic Correlation.*—These anatomic lesions may be correlated with the essential features of the syndrome, of which the classic components present in this case were ipsilateral signs of cerebellar involvement; contralateral sensory disturbances consisting of loss of pain and temperature sense, with no disturbance of other forms of sensation, and, at times, ipsilateral involuntary movements.

In addition, we observed, ipsilateral weakness of the face in smiling, with contralateral weakness in the wincing reaction; contralateral deafness, and ipsilateral paralysis of sympathetic fibers.

The ipsilateral cerebellar signs, which in our patient consisted of hypotonia, ataxia, dysmetria, asynergia, adiadokokinesis, rebound phenomenon, intention tremor and dysarthria, are explained by lesions in the cerebellar hemisphere, dentate nucleus and brachium conjunctivum.

The contralateral loss of pain and temperature sensation is the result of degeneration of the spinothalamic tract, which is located in the dorsolateral region of the pontile tegmentum. The medial lemniscus itself derives its blood supply from pontile branches of the basilar artery. Only the most lateral portion, with its spinothalamic component, is supplied by the superior cerebellar artery. Hence, other forms of sensation were unimpaired while pain sense and temperature sense were lost. As pointed out by Russel, it is inaccurate to term this a syringomyelic type of sensory disturbance, as has been the custom, since in syringomyelia the *areas* involved are dissociated, while with spinothalamic lesions the whole side is affected.

In addition to the classic features of the syndrome, other symptoms have been described in previous reports, and still others were unique in our case. It should be repeated here that several small lesions seen in our sections in the subcortex, corpora striata and hypothalamus were probably the result of multiple small emboli, characteristic of subacute bacterial endocarditis.

1. Contralateral facial mimetic paralysis with unimpaired voluntary facial movements was seen in the cases of Mills [1a] and Russel,[1e] and the latter ascribed this symptom to a lesion in the caudate nucleus. Wilson [5] considered this symptom in his discussion of pathologic laughing and crying and the faciorespiratory synkinesis. The existence of separate central pathways for voluntary and involuntary movements in the faciorespiratory mechanism explains the involvement of one type without the other. In our patient there was contralateral mimetic paralysis in

5. Wilson, S. A. K.: Pathological Laughing and Crying, in Modern Problems in Neurology, New York, William Wood & Company, 1929, chap. 12.

wincing, with unimpaired voluntary movement. In addition, there was ipsilateral weakness in smiling, which is difficult to explain if the smiling represented true involuntary movement on the contralateral side, as was apparently the case.

The central tegmental fasciculus, degeneration of which is outstanding in our sections, has been suggested as a possible factor in the facio-respiratory mechanism. One of us [6] has indicated this relationship in a previous discussion of palatal myoclonus, which symptom, incidentally, may have been present in our patient, but on this point the clinicians were uncertain. Clonic movements of the jaw occurred, however, and this has been considered an analogous symptom.

Van Bogaert and Bertrand [7] cited evidence in support of the concept of a crossed dentatorubro-olivary system, of which the central tegmental fasciculus may be one of the principal groups of fibers, but which may include the brachium conjunctivum and reticular substance of the tegmentum, as well as other structures. They indicated the anatomic evidence from numerous observations pointing to the dentato-olivary system as the primary one involved in several myoclonic syndromes and suggested that myoclonus and tremor represent an abnormal motor discharge due to anatomic or functional release from the extrapyramidal inhibitory mechanism. In our sections, we have demonstrated degeneration involving the several components which may constitute such a pathway. It should be noted that the degeneration was seen in the ipsilateral central tegmental fasciculus and the contralateral inferior olive. The former was involved directly by infarction with subsequent degeneration; the latter, simply as a result of retrograde degeneration, corresponding to the destruction of the opposite dentate nucleus.

2. Contralateral deafness was observed by Mills. The lesion involving the lateral lemniscus which we have demonstrated explains this symptom, although local causes were not ruled out. Hearing was somewhat impaired ipsilaterally in our case, possibly as a result of infarction in the region near the cochlear nucleus.

3. Horner's syndrome has not been described in any of the previous cases. The reports of Ranson and his co-workers [8] on the higher connections of the sympathetic nervous system indicate that the descending connections from the hypothalamus are distributed over a wide area in the central and tegmental regions of the midbrain, and that if any con-

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6. Freeman, W.: Palatal Myoclonus, Arch. Neurol. & Psychiat. **29**:742 (April) 1933.

7. van Bogaert, L., and Bertrand, I.: Sur les myoclonies associées synchrones et rhythmiques par lésions en foyer du tronc cérébrale, Rev. neurol. **35**:203, 1928.

8. Magoun, H. W.; Ranson, S. W., and Hetherington, A.: Descending Connections from the Hypothalamus, Arch. Neurol. & Psychiat. **39**:1127 (June) 1938.

centration of these pathways occurs at the pontile level, the probable location is in the tegmentum. This was the area of the brain stem involved by the infarction in our sections.

4. Palsy of the sixth nerve occurred in cases 6 and 7 of Davison's group and in cases 1 and 4 of Critchley and Schuster. It was thought that an anomalous distribution of the artery to the nucleus of the sixth nerve may have been the cause, and the possibility of implication of the pontile branches of the basilar artery was also considered. The nucleus is not clearly involved in our sections, although some darkening is seen in the region of the median longitudinal fasciculus and at the genu of the facial nerve.

5. Increased tendon reflexes, Hoffmann and Babinski signs, nuchal rigidity and a Kernig sign were seen clinically. These were probably manifestations of the small embolic foci independent of the main lesion.

6. Several atypical features have been reported in previous cases, such as: involvement of the medial lemniscus; involvement of the spinothalamic tract without loss of pain and temperature sensation; contralateral involuntary movements, and variability in nystagmus and past pointing reactions on labyrinthine stimulation.

These phenomena have been discussed in the report of Critchley and Schuster, and their consideration is outside the realm of the present paper.

## SUMMARY

A case of occlusion of the superior cerebellar artery is presented, with correlation of the clinical picture and the postmortem observations. The classic aspects of the syndrome of the superior cerebellar artery are reviewed, and some atypical features are discussed with a view to correlating the anatomic lesions and indicating some problems of functional localization.

# Case Reports

## MARCUS GUNN PHENOMENON

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Marcus Gunn,[1] in 1883, reported a case of "congenital ptosis with peculiar associated movements of the affected lid" in a girl of 17. At the age of 5 weeks, when the infant was suckling, it was noted that the ptosed lid "nearly went up out of sight" with each movement of the jaw. There had been improvement in this affliction during the two or three years prior to her observation by Gunn.

There were slight facial asymmetry and ptosis to the degree that the lid covered the upper quarter of the left pupil; the fold of the left upper lid was oblique as compared with that of the right, which ran parallel to the free border. The left pupil was smaller than the right. The pupillary reactions, however, were all normal. No other components of a Horner syndrome were present. There was synchronous movement of the upper lid with upward and downward movement of the globe. With upward gaze the upper lid did not rise as high on the left side as on the right. Closure of the left eye was not as perfect as that of the right. Any voluntary elevation of the left eyelid was not possible without the aid of the frontalis muscle. This supplementary muscular action only slightly diminished the ptosis. Movement of the jaw to the right (action of the left external pterygoid muscle) caused concomitant elevation of the left lid, which was maintained as long as the activating muscle was at work. Protrusion of the jaw caused a similar phenomenon. The greatest excursion in both instances was effected with downward gaze. Action of the levator palpebrae muscle was visible beneath the skin folds when the left external pterygoid muscle was activated and the eyes were closed. No movement of the eye or pupil was noted during the upward movement of the lid.

These observations recorded by Gunn and checked by a committee of three neurologists and one ophthalmologist still stand as the essential criteria for the syndrome now named after him. This phenomenon is also commonly referred to as the "jaw winking reflex." Rare cases

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1. Gunn, M.: Congenital Ptosis with Peculiar Associated Movements of the Affected Lid, Tr. Ophth. Soc. U. Kingdom **3**:283, 1883.

have been described in which involuntary elevation of the eyelid has been associated with action of the opposite orbicularis oculi muscle, a homolateral extraocular muscle, extreme generalized muscular effort or action of a muscle innervated by the seventh or ninth nerve. In a small percentage, roughly 5 to 7, of the cases in the literature the condition was said to be acquired. Over 80 per cent of the cases are almost identical with the one originally described by Gunn. Thorough reviews of the literature have been made by Sinclair,[2] Lutz,[3] Cazin [4] and Grant.[5]

We shall report 3 cases: the first, an instance of the phenomenon in an infant 5 months old; the second, a typical case comparable in many ways to that originally described by Gunn, and the third, an instance of the phenomenon in a patient with jacksonian epilepsy. The third case is of particular interest because it is, we believe, the first instance to be recorded in the literature in which the Marcus Gunn phenomenon was elicited by cortical stimulation.

## REPORT OF CASES

CASE 1.—A girl aged 5 months was admitted with the complaint of persistent vomiting since birth. The abnormal movements of the eyelid were not noted by the family, who see no change in her appearance at present. She is still in the hospital under treatment for active rickets, scurvy and interstitial pneumonia. In the ward it was noted that during feeding there were abnormal movements of the right eyelid synchronous with sucking movements of the mouth. Nothing else in the physical examination suggested any disorder not directly related to the malnutrition and infection. Movements of the eyelid, which are shown in figure 1, are characteristic of so-called jaw winking.

CASE 2.—The patient was delivered at full term after ten hours of vigorous labor. Forceps were used, and it was reported that the "right temple was cut just in front of the ear." Ptosis of the right eye was noted immediately after birth. No definite information concerning peripheral palsy of the facial nerve could be obtained. There was, however, occasional twitching of the right side of the face, which was interpreted as a sign of an old injury of the facial nerve. As soon as the patient was suckled, it was noted that with each movement of the jaw the right upper eyelid was elevated to such an extent that the "white could be seen above the pupil."

The family and the developmental histories were noncontributory.

During the last two or three years the ptosis had decreased to a slight extent, but the associated movement persisted. Medical aid was sought because the patient, who, at the age of 8½ years, was a good student and an outstanding boy at school, was becoming sensitive as the result of the jests and remarks of his contemporaries concerning his affliction. This stigma was assuming such importance that he would eat with strangers only under duress.

Physical examination revealed a well developed and well nourished boy who appeared normal except for ptosis of the right eyelid. This was overcome by

2. Sinclair, W. W.: Abnormal Associated Movements of the Eyelids, Ophth. Rev. **14**:307, 1895.

3. Lutz, A.: Jaw Winking Phenomenon and Its Explanation, Arch. Ophth. **48**:144, 1919.

4. Cazin, L.: Le phénomène de Marcus Gunn; mâchoire à clignements, Thesis, Paris, 1928.

5. Grant, F. C.: The Marcus Gunn Phenomenon: Report of a Case with Suggestions as to Relief, Arch. Neurol. & Psychiat. **35**:487 (March) 1936.

deviation of the jaw to the left or midline depression of the mandible. Ineffectual contraction of the levator palpebrae muscle took place under the skin and folds of the orbicularis oculi muscle when these jaw movements were carried out with the eyes voluntarily closed. Gentle passive depression or deviation of the mandible did not cause an associated movement of the eyelid. Firm movement, however, did.

Laboratory studies revealed nothing of significance.

As may be seen in figure 2, the phenomenon in this case is almost a mirror image of that in the original case described by Gunn.

Fig. 1 (case 1).—Elevation of the right lid synchronous with sucking movements.

Electroencephalographic tracings recorded two wave and spike excursions and many slow waves during hyperventilation. A pneumoencephalogram revealed no enlargement or distortion of the ventricular or the subarachnoid system. With these findings we felt justified in carrying out only a plastic procedure on the eyelid, hoping thereby to obscure, so far as possible, the upward movement of the right upper eyelid which was synchronous with the movements of the lower jaw previously described.

CASE 3.—A boy, now aged 9 years 4 months, was born at term by vertex presentation. Delivery was effected with forceps at the end of forty-eight hours

Fig. 2 (case 2).—Ptosis of the right lid with the jaw at rest; no change in ptosis with deviation of the jaw to the right; absence of ptosis with deviation of the jaw to the left; absence of ptosis with midline depression of the mandible.

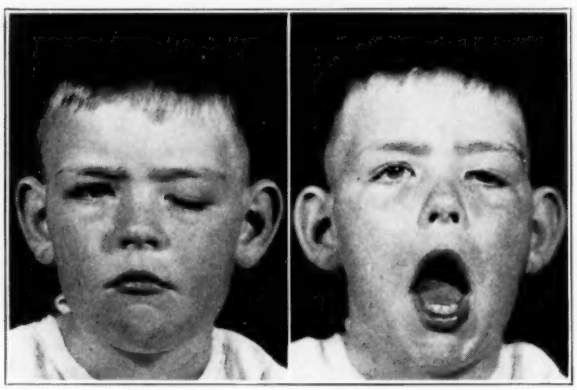

Fig. 3 (case 3).—Ptosis of the left lid with the jaw at rest; diminution of ptosis with midline depression of the jaw.

of labor. Respirations began spontaneously. There was considerable molding of the head. Complete ptosis of the left eye was noted at birth. Twelve hours later the patient became cyanotic, for relief of which he was kept in an atmosphere of oxygen for three days. From that time his general development was considered normal.

A suspension operation was carried out on the left eye at the age of 3 years in another hospital. Unfortunately, this was complicated by wound sepsis, and no appreciable benefit was derived.

The patient was originally thought to be left handed. He is now right handed. He has always stuttered to a certain extent, but this has increased during the two years previous to his admission to the Children's Hospital. Since infancy his family has noted that the ptosed eyelid becomes elevated when he is frightened or enraged. In spite of stuttering and ptosis, the patient has done satisfactorily in school.

In November 1938 the patient was studied in the neurologic service of the Children's Hospital. A diagnosis of jacksonian epilepsy was made.

Pneumoencephalographic examination revealed enlargement of the left lateral ventricle. There was no enlargement or distortion of the right lateral or the third ventricle. A moderate amount of air spread over the cortex. Repeated electroencephalographic tracings revealed a focus of irritation in the right parietal region. We interpreted the enlargement of the left lateral ventricle as a residual of an old birth injury or of asphyxia at the time of birth. No history of trauma or of severe illness could be obtained. The family history revealed no evidence of syphilis, epilepsy, alcoholism or allergy.

A medical regimen was tried for sixteen months, with fair success at first. However, during a period of three months before the last admission to the hospital the attacks became more severe and frequent. Sensory attacks occurred as often as ten times daily. Motor attacks, with clonic and tonic movements, occurred two to three times weekly. Exploration of the right parietal cortex was therefore decided on.

The boy's speech was initiated by forceful opening and closing of the jaw accompanied by crude vocalization, which hindered intelligible production of sound. During this process each forceful downward movement of the jaw was associated with a synchronous elevation of the ptosed eyelid. This convinced us that we were dealing with two conditions, the Marcus Gunn syndrome and jacksonian epilepsy.

Physical examination revealed that the boy was well developed and well nourished and mentally alert. There was complete ptosis of the left eyelid, which was only slightly overcome by violent effort on the part of the corresponding frontalis muscle. Marked voluntary midline depression of the mandible caused the greatest diminution in the ptosis; lateral deviation of the jaw produced no change in the degree. The pupils were round, regular and equal; they reacted equally to light and in accommodation. There was slight enophthalmos on the left. The extraocular movements on the right were normal. On the left there was palsy of the lateral and superior rectus muscles as well as of the inferior oblique. The other extraocular muscles on that side functioned normally. All other cranial nerves were intact. The optic disks showed no signs of increased pressure. Vision was 12/30 in the right eye and 2/200 in the left eye.

The tendon reflexes were all present but sluggish. The abdominal and cremasteric reflexes were present and active. The Babinski reaction was negative. Sensation was everywhere intact.

Examination of the ears, nose, throat, gastrointestinal tract and genitourinary and cardiorespiratory systems revealed no abnormality.

Laboratory studies showed nothing significant.

It was hoped that in the process of identifying a trigger area for excision an opportunity would be afforded to stimulate the jaw and eyelid areas recently mapped out by Penfield and Boldrey.[6]

A large osteoplastic bone flap was turned down in the right parietal region, without event. The dura was normal in appearance. There were no subdural adhesions. There was slight but perceptible thickening of the arachnoid at the

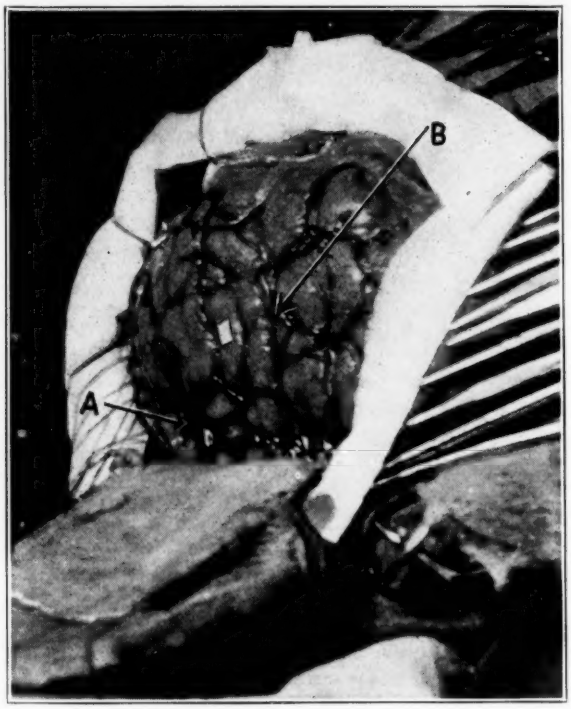


Fig. 4 (case 3).—Photograph of the right cortex exposed at operation. Note white marker on the trigger area, (*A*) with an arrow pointing to vessels in the region of the sylvian fissure and (*B*) an arrow pointing to the rolandic fissure.

junction of the rolandic and the sylvian fissure. In the region of the latter the vessels stood out somewhat more prominently than usual, as may be seen in the photograph of the exposed cortex (fig. 4 *A*). Scattered areas of just perceptible arachnoiditis lay anterior to the premotor area. Systematic stimulation of the entire area of cortex exposed was carried out, while synchronous movements of

6. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**:389, 1937.

the jaw and ptosed eyelid were observed by one of us. Jaw winking was elicited in the areas marked with crosses (fig. 5), as well as over the entire surface of the gyrus indicated in the photograph (fig. 4) and the diagram (fig. 5). No areas were found from which movement of the eyelid alone could be elicited. Seizures were also repeatedly produced by faradic and galvanic stimulation of this gyrus. A concomitant elevation of the ptosed eyelid preceded the onset of the seizures, which spread downward from the angle of the mouth to the foot. Accordingly, this area was excised, all major vessels at its periphery being spared. After satisfactory hemostasis the wound was closed. The entire procedure was carried out with a 0.5 per cent solution of procaine hydrochloride and light anesthesia induced by avertin with amylene hydrate supplemented with ether. During the process of stimulation the patient was practically awake.

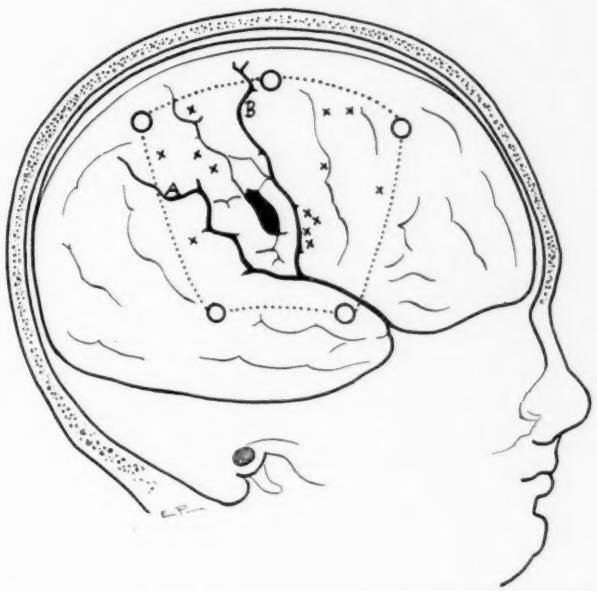


Fig. 5 (case 3).—Diagram of the right cortex exposed. Solid black indicates the trigger area excised at operation, corresponding with the gyrus (white marker) in figure 2 (jaw winking was ubiquitous in this area); *X*, scattered areas where stimulation elicited jaw winking. *A* marks the sylvian fissure, and *B*, the rolandic fissure.

Histologic examination of the tissue removed revealed evidence of thickening and fibrosis of the pia overlying the brain. Several of the pial vessels showed thickening of their walls. No gliosis was seen.

The patient's recovery was uneventful. One hour after operation, when the patient was cooperative and responsive, the jaw winking was more pronounced than ever and remained so for forty-eight hours. By the second postoperative day synchronous movement of the ptosed eyelid with midline depression of the mandible had gradually returned to its usual form.

We believe that the lessened inhibition of the jaw winking during the first forty-eight hours after operation was due to release from cortical control resulting from the anesthesia and local edema in the region of the extirpated trigger area.

## SUMMARY

Three cases of the Marcus Gunn phenomenon are reported, the third being of special interest because the reaction was produced by cortical stimulation.

We believe that a tenable theory for the Marcus Gunn phenomenon can be postulated on the basis of comparative anatomy and physiology. This, with experimental work now in progress, will be reported on later.

# News and Comment

## THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

At a meeting of the American Board of Neurological Surgery held in Philadelphia, June 6 and 7, 1941, the following diplomates were certified:

Alexander T. Bunts; Ralph B. Cloward; Edwin M. Deery; W. de Gutierrez-Mahoney; Dean Echols; Thomas S. P. Fitch; Robert L. Glass; Nicholas Gotten; Sidney W. Gross; Elisha S. Gurdjian; Thomas I. Hoen; Olan R. Hyndman; Carl F. List; Nathan C. Norcross; John Raaf; William B. Scoville; I. M. Tarlov; Frank Turnbull; Harold C. Voris, and Harry Wilkins.

The following is a complete list of diplomates to date:

| Name | Address | Certification Date |
|---|---|---|
| 1. Adson, Alfred W. | Mayo Clinic, Rochester, Minn. | July 1940 |
| 2. Anderson, Gilbert C. | 3431 Prytania St., New Orleans | July 1940 |
| 3. Bagley, Charles, Jr. | 2 E. Reed St., Baltimore | Oct. 1940 |
| 4. Bailey, Percival | 1853 W. Polk St., Chicago | July 1940 |
| 5. Bradford, F. Keith. | Medical Arts Bldg., Houston, Texas | Oct. 1940 |
| 6. Browder, E. Jefferson. | 200 Hicks St., Brooklyn | Sept. 1940 |
| 7. Bucy, Paul C. | 25 E. Washington St., Chicago | July 1940 |
| 8. Bunts, Alexander T. | Cleveland Clinic, Cleveland | June 1941 |
| 9. Cleveland, David. | 324 E. Wisconsin Ave., Milwaukee | Oct. 1940 |
| 10. Cloward, Ralph B. | Alex. Young Bldg., Honolulu, Hawaii | June 1941 |
| 11. Coburn, Donald F. | 700 W. 47th St., Kansas City, Mo. | Oct. 1940 |
| 12. Cohen, Ira. | 4 E. 95th St., New York | July 1940 |
| 13. Coleman, Claude C. | Professional Bldg., Richmond, Va. | Sept. 1940 |
| 14. Craig, Winchell McK. | Mayo Clinic, Rochester, Minn. | July 1940 |
| 15. Crawford, Albert S. | Ford Hospital, Detroit | July 1940 |
| 16. Crutchfield, Gayle. | Professional Bldg., Richmond, Va. | July 1940 |
| 17. Dandy, Walter E. | Johns Hopkins Hospital, Baltimore | Oct. 1940 |
| 18. Davidoff, Leo M. | 557 Prospect Place, Brooklyn | July 1940 |
| 19. Davis, Loyal. | 54 E. Erie St., Chicago | July 1940 |
| 20. Deery, Edwin M. | 563 Park Avenue, New York | June 1941 |
| 21. de Gutierrez-Mahoney, W. | Vanderbilt University Hospital, Nashville, Tenn. | June 1941 |
| 22. Echols, Dean. | American Bank Bldg., New Orleans | June 1941 |
| 23. Ehrlich, William. | 31 Lincoln Park, Newark, N. J. | Oct. 1940 |
| 24. Evans, Joseph Patrick. | Cincinnati General Hospital, Cincinnati | Oct. 1940 |
| 25. Fay, Temple. | Temple University Hosp., Philadelphia | July 1940 |
| 26. Fincher, Edgar F. | 384 Peachtree St., Atlanta, Ga. | July 1940 |
| 27. Fitch, Thos. S. P. | 916 Park Ave., Plainfield, N. J. | June 1941 |
| 28. Fleming, Howard W. | 384 Post St., San Francisco | July 1940 |
| 29. Furlow, Leonard T. | University Club Bldg., St. Louis | July 1940 |
| 30. Gardner, W. James. | 2050 W. 93d St., Cleveland | July 1940 |
| 31. German, William. | New Haven Hosp., New Haven, Conn. | Sept. 1940 |
| 32. Glass, Robert L. | Hume Mansur Bldg., Indianapolis | June 1941 |
| 33. Gotten, Nicholas. | 188 S. Bellevue Blvd., Memphis, Tenn. | June 1941 |
| 34. Grant, Francis C. | 3400 Spruce St., Philadelphia | July 1940 |
| 35. Groff, Robert A. | 255 S. 17th St., Philadelphia | Oct. 1940 |
| 36. Gross, Sidney W. | 8 E. 83d St., New York | June 1941 |
| 37. Gurdjian, Elisha S. | 840 David Whitney Bldg., Detroit | June 1941 |

38. Gustafson, Wesley Axel....30 N. Michigan Ave., Chicago.....Oct. 1940
39. Hamby, Wallace B.....140 Linwood Ave., Buffalo.....Oct. 1940
40. Haven, Hale.....Mason Clinic, Seattle.....Oct. 1940
41. Hoen, Thomas I.....New York Medical College, New York..June 1941
42. Hermann, Jess D.....1214 Med. Arts Bldg., Oklahoma City...Oct. 1940
43. Horrax, Gilbert.....Lahey Clinic, Boston.....Sept. 1940
44. Hyndman, Olan R.....State University of Iowa, Iowa City....June 1941
45. Ingraham, Franc D.....300 Longwood Ave., Boston.....July 1940
46. Jones, Ottiwell W.....University of California Hospital, San Francisco.....July 1940
47. Kahn, Edgar.....University Hospital, Ann Arbor, Mich...Oct. 1940
48. Keegan, J. J.....1234 Medical Arts Bldg., Omaha.....Sept. 1940
49. Klemme, Roland.....4952 Maryland Ave., St. Louis.....Oct. 1940
50. List, Carl F.....University Hospital, Ann Arbor, Mich..June 1941
51. Love, J. Grafton.....Mayo Clinic, Rochester, Minn.....July 1940
52. Lyerly, James G.....514 Greenleaf Bldg., Jacksonville, Fla....July 1940
53. Mayfield, Frank.....802 Carew Tower, Cincinnati.....Oct. 1940
54. Masson, Clement B.....Neurological Institute, New York.....July 1940
55. Mixter, William Jason.....319 Longwood Ave., Boston.....July 1940
56. Morrissey, Edmund J.....909 Hyde St., San Francisco.....July 1940
57. Munro, Donald.....818 Harrison Ave., Boston.....July 1940
58. Murphey, Francis.....899 Madison Ave., Memphis, Tenn.....Oct. 1940
59. Naffziger, Howard C.....384 Post St., San Francisco.....July 1940
60. Norcross, Nathan C.....2001 Collingwood Ave., Toledo, Ohio...June 1941
61. Oldberg, Eric.....University of Illinois College of Medicine, Chicago .....July 1940
62. Peet, Max Minor.....University Hospital, Ann Arbor, Mich...July 1940
63. Peyton, William T.....University of Minnesota Hospital, Minneapolis .....Oct. 1940
64. Pilcher, Cobb.....Vanderbilt University Hospital, Nashville, Tenn.....July 1940
65. Putnam, Tracy J.....Neurological Institute, New York.....July 1940
66. Raaf, John.....912 Medical Dental Bldg., Portland, Ore..June 1941
67. Rand, Carl W.....1023 Pacific Mutual Bldg., Los Angeles..July 1940
68. Raney, Rupert B.....727 W. 7th St., Los Angeles.....Oct. 1940
69. Reeves, David Lander.....2210 W. 3d St., Los Angeles.....Oct. 1940
70. Rowe, Stuart N.....4800 Friendship Ave., Pittsburgh.....Oct. 1940
71. Sachs, Ernest.....University Club Bldg., St. Louis.....July 1940
72. Scarff, John E.....Neurological Institute, New York.....Oct. 1940
73. Schnitker, Max T.....2360 E. Monroe St., Toledo, Ohio.....April 1941
74. Schreiber, Frederic.....10 Peterboro St., Detroit.....Oct. 1940
75. Scott, Michael.....Temple University Hosp., Philadelphia...Oct. 1940
76. Scoville, William B.....179 Allyn St., Hartford, Conn.....June 1941
77. Semmes, Eustace.....899 Madison Ave., Memphis, Tenn.....Sept. 1940
78. Shelden, Charles Hunter...1930 Wilshire Blvd., Los Angeles.....Oct. 1940
79. Snodgrass, Samuel Robert.814 Avenue B, Galveston, Texas.....Oct. 1940
80. Spurling, R. Glen.....404 Brown Bldg., Louisville, Ky.....July 1940
81. Stookey, Byron.....Neurological Institute, New York.....July 1940
82. Tarlov, I. M.....175 Eastern Parkway, Brooklyn.....June 1941
83. Teachenor, Frank.....730 Professional Bldg., Kansas City, Mo...July 1940
84. Turnbull, Frank.....Medico-Dental Bldg., Vancouver, British Columbia, Canada.....June 1941
85. Van Wagenen, William P..Strong Memorial Hospital, Rochester, N. Y.....July 1940
86. Voris, Harold C.....Columbus Memorial Bldg., Chicago.....June 1941
87. Walker, Arthur Earl.....950 E. 59th St., Chicago.....Oct. 1940
88. Wilkins, Harry.....Medical Arts Bldg., Oklahoma City.....June 1941

## POSTGRADUATE INSTITUTE FOR STATE HOSPITALS

The third regional postgraduate institute for state hospitals was held at the South Carolina State Hospital, Columbia, S. C., from April 14 to 26. The institute was under the sponsorship of the American Psychiatric Association, through its Committee on Psychiatry in Medical Education, and was financed by a grant from the Rockefeller Foundation. The average daily attendance was 55, with a total registration of 78. Sixteen states were represented. A variety of subjects were discussed, including neuroanatomy, neuropathology, psychobiology, psychotherapy, neuroroentgenology, neuro-ophthalmology, neurosurgery, electroencephalography, clinical psychiatry, clinical neurology and a group of related subjects.

The fourth institute will be held at the Western State Hospital, Fort Steilacoom, Wash., from Sept. 1 to 13, 1941. Those interested in attending the coming institute should communicate with either Dr. William N. Keller, superintendent, Western State Hospital, Fort Steilacoom, Wash., or Dr. Franklin G. Ebaugh, Colorado Psychopathic Hospital, Denver.

## NEW PUBLICATIONS

A German translation of Clifford W. Beer's autobiography, "A Mind That Found Itself," which has gone through many editions in the United States (it is now in its twenty-fifth printing) and is still widely read, has just been published under the title *"Eine Seele, die sich wiederfand,"* imprint of Benno Schwabe & Company, Basel, Switzerland. The translator is Otto Reuter, and Dr. Heinrich Meng, professor of psychiatry at the University of Basel, contributes a preface jointly with Dr. André Repond, president of the Swiss National Committee for Mental Hygiene. Appearing for the first time in the German language, the book has been widely and enthusiastically reviewed in German professional periodicals, the *Heilpedagogische Werkblätter* hailing it as a masterpiece "deserving a place among the classics of world literature." The proceeds from the sale of the work will be devoted to the development of the mental hygiene program in Switzerland. The only previous foreign translations of the story are those which appeared in Czech, in 1937, and in Portuguese, in 1934, and Dr. Meng hopes that editions will be issued, as soon as conditions permit, in French, Hungarian and Dutch. In their foreword, Drs. Meng and Repond pay tribute to Beers's unique achievements, as founder of the mental hygiene movement, and express the wish that his book "will arouse in many a sense of responsibility for the fate of those threatened by mental illness, and the will to help them," remarking also on its value to the scientist as a rare psychologic document.

**American Psychiatric Association.**—At the annual meeting of the American Psychiatric Association, May 5 to 9, 1941, the following officers were elected: J. K. Hall, M.D., president, Richmond, Va.; Arthur H. Ruggles, M.D., president-elect, Providence, R. I., and Winfred Overholser, M.D., secretary-treasurer, Washington, D. C.

# Abstracts from Current Literature

## Anatomy and Embryology

THE ANATOMICAL RELATIONSHIPS OF THE HYPOPHYSIAL STEM AND THE MEDIAN EMINENCE. T. A. WEAVER JR. and P. C. BUCY, Endocrinology **27**:227 (Aug.) 1940.

Recent physiologic observations pertaining to the exact location of lesions producing diabetes insipidus have made desirable an accurate definition of the line of junction of the neurohypophysis and the hypothalamus. The authors report on a study of 9 monkey (Macacus rhesus) and 4 cat brains in which the hypothalamus and the intact attached hypophysis were cut and stained serially by several staining methods in order to bring out the cytologic differences between these two areas.

The delineation of the neurohypophysis was based on the presence in this tissue of the pituicyte, a cellular element which is peculiar in its morphologic and staining characteristics and is found nowhere else in the nervous system. On the basis of their studies the authors conclude that most of the posterior portion of the median eminence lying posterior to the third ventricle contains cellular elements peculiar to the neurohypophysis and should be considered a part of the pars nervosa. The anterior portion of the median eminence lying anterior to the third ventricle cannot be said to be thus closely related to the neurohypophysis, and the portion superior to a clearly defined division must be considered part of the tuber cinereum of the hypothalamus. The pars tuberalis is not always coexistent with the neurohypophysis.

PALMER, Philadelphia.

CERTAIN BASAL TELENCEPHALIC CENTERS IN THE CAT. CLEMENT A. FOX, J. Comp. Neurol. **72**:1 (Feb.) 1940.

The material for this study included the brains of cats cut serially in either transverse or sagittal planes and stained with toluidine blue, by Weil's method for myelin or by a silver impregnation technic. Fox studied chiefly the olfactory system and related parts. A blotting paper model of the tuberculum olfactorium was constructed to show the arrangement of the islands of Calleja. The primary, secondary and tertiary olfactory centers of the cat were found to be well developed. The amygdala consisted of three nuclear groups, of which the lateral group was closely associated with the external capsule and at its posterior end received corticoamygdaloid fibers by way of the external capsule from areas of the cortex other than the pyriform cortex. The lateral nucleus sent fibers through the external capsule to join the posterior limb of the anterior commissure. Other amygdaloid connections were with the nucleus entopeduncularis and the preoptic area, as well as with the stria terminalis and the longitudinal association bundle.

ADDISON, Philadelphia.

DIFFERENTIATION OF THE BULBAR MOTOR NUCLEI AND THE COINCIDENT DEVELOPMENT OF ASSOCIATED ROOT FIBERS IN THE RABBIT. DONALD L. KIMMEL, J. Comp. Neurol. **72**:83 (Feb.) 1940.

This is a study of the ontogenic development of the nuclear centers of bulbar cranial nerves in the rabbit and of the embryonic and adult distribution of their branches. Series of brains of embryonic, young and adult rabbits were studied after being cut in various planes and prepared by a silver impregnation technic or with toluidine blue. A detailed account is given of the differentiation of the bulbar efferent cranial nerve nuclei and of the development of their peripheral branches from the 11 day old embryo to the adult. A definite segmentation was

seen in the gray substance of the brain stem of young embryos, and each of the neuromeres contributed fascicles to one or more cranial nerves. The efferent roots of the cranial nerves had their origin from a common efferent cell column, which was continuous throughout the brain stem and extended caudally into the spinal cord. At first this cell column differentiated into a somatic efferent and a common visceral efferent column, with the somatic efferent cells located medial to the visceral efferent gray column. Some of the larger multipolar cells of the common visceral efferent column began to migrate ventrolaterally and formed the special visceral efferent column. The differentiation of the special visceral efferent cell column was simultaneous with the differentiation of the mesenchyme into primordial muscle groups. As migration into the special visceral efferent gray column was nearing completion, the columns separated into nuclear groups, and the various cell groups of the subdivisions of the cranial nerves were formed. There was a high degree of interrelation between the nuclear and fiber differentiation of the medulla oblongata and the stage of development of the peripheral motor mechanism.

FRASER, Philadelphia.

SUPRA-AND POST-OPTIC COMMISSURES IN THE BRAIN OF THE RAT. YÜ-CH'UAN TSANG, J. Comp. Neurol. **72**:535 (June) 1940.

Tsang blinded 4 rats in one or both eyes at birth or on the thirteenth day of life and killed them seven months later. Two more rats were killed three months after similar operations, when 4 months old. The brains were cut transversely and prepared to demonstrate myelinated fibers. In the bilaterally blinded animals no trace of optic fibers was recognizable after seven months. Seven commissures are described. The outstanding ones are those of Gudden, Meynert and Ganser. Gudden's commissure begins at the posterior third of the optic chiasm and extends farther caudally than the chiasm itself. Gudden's commissure is a true commissure in that it connects corresponding contralateral structures—the optic thalamus and the optic tectum. Meynert's commissure is dorsocaudal to Gudden's commissure. This commissure is not a true commissure. It connects the contralateral corresponding structures on the ventral and lateral surfaces of the thalamus and on the dorsal surface of the midbrain. It receives fibers successively from the fasciculus suprachiasmaticus, the anterior and lateral hypothalamic nuclei, the nucleus supraopticus diffusus, the cerebral peduncle, the globus pallidus, the subthalamic regions, the deeper parts of the thalamus, the lateral and medial geniculate bodies, the pretectal nuclei and the tectum mesencephali. In addition, some fibers originating from the nucleus supraopticus diffusus do not cross the midline. Ganser's commissure is dorsocaudal to Meynert's and below the floor of the third ventricle in the chiasmatic ridge. This commissure is composed of three fascicles: an anterior fascicle, starting in the vicinity of the ventral extension of the interstitial nucleus of the stria terminalis; a middle fascicle, which radiates dorsolaterally between the columns of the fornix and the olfactohypothalamic tract, and a posterior fascicle, which reaches the lower border of the medial extension of the zona incerta. There are four minor crossed bundles in the supraoptic and postoptic regions: the suprachiasmatic decussation, the periventricular commissure, which connects the periventricular nuclei, the dorsal tuberal commissure and the ventral tuberal commissure, which connects the ventrocaudal parts of the hypothalamus.

FRASER, Philadelphia.

PARTIAL AGENESIS OF THE CEREBELLUM IN DOGS. ROBERT S. DOW, J. Comp. Neurol. **72**:569 (June) 1940.

This report is based on the study of 2 Boston bull terriers which were born of normal parents. The abnormality of their motor activity was noticed shortly after birth, and they were studied by Dow from the time they were 3 months 11 days old until their death, about six and seventeen months later. The brains were prepared for the study of myelin, Nissl substance and vascular structures.

The symptoms of cerebellar deficiency were almost identical in the 2 animals. This syndrome consisted of increased positive supporting reactions, tremor of the head, dysmetria of the movements of the extremities and some abnormalities in the placing and hopping reactions. The agenesis was essentially the same in the 2 animals and consisted in the absence of the greater part of the culmen and complete loss of the middle lobe of the vermis, the pyramis, the uvula, the nodulus and the right lobulus paramedianus. The fastigial nuclei were almost completely missing, and the nuclei interpositi were very small. The left dentate nucleus was apparently normal, while the right was reduced in size. The superior and inferior cerebellar peduncles were smaller than normal, while the middle cerebellar peduncle apparently was of normal size. The nerve cells of the inferior olivary nucleus were atrophied on both sides.

ADDISON, Philadelphia.

A QUANTITATIVE AND EXPERIMENTAL STUDY OF THE CERVICAL SYMPATHETIC TRUNK. JAMES O. FOLEY and FRANKLIN S. DUBOIS, J. Comp. Neurol. **72**:587 (June) 1940.

In 6 adult cats, after laminectomy, different groups of dorsal and ventral roots were sectioned close to the spinal cord on the left side. In 5 other cats the ganglia of the spinal nerves were removed and the ventral roots sectioned. The animals were allowed to survive from nine to one hundred and seven days. The upper cervical portion of the sympathetic trunk was prepared for microscopic study by a variety of methods, including silver impregnation technics. Counts of axons and of myelin sheaths were made. In the intact nerves 5,404 to 10,076 axons were enumerated, of which 20 to 73 per cent were unmyelinated. There were no significant differences in the numbers of fibers in the upper cervical portion of the sympathetic trunk of the cat after ventral radicotomy alone and after ventral radicotomy plus dorsal ganglionectomy of appropriate thoracic nerves. Foley and DuBois conclude that if afferent fibers are present in the cervical portion of the sympathetic trunk they are not frequent enough to be detected by the methods employed.

FRASER, Philadelphia.

THE RESPIRATORY CENTER AND ITS DESCENDING PATHWAYS. R. F. PITTS, J. Comp. Neurol. **72**:605 (June) 1940.

Using a series of sections of medulla stained for cells, Pitts has compared the location of respiratory responses in relation to cell groups in the medulla of the cat. The inspiratory center was identified within the ventral portion of the reticular formation overlying the cephalic four fifths of the inferior olive. The expiratory center was in the dorsal reticular formation overlying the inspiratory center. In a number of cats electrolytic lesions were placed at various points in the medulla. After a period of from twelve to eighteen days the brains and spinal cords were prepared by the Marchi technic. No single lesion was uncomplicated by encroachment on some known or unknown descending pathway. However, Pitts was able to determine that lesions in the inferior reticular nucleus were followed by degeneration in the anterior and anterolateral columns of the spinal cord, usually ipsilateral. Partial section of the spinal cord at the level of the first cervical region was performed. After the operation and at intervals up to the tenth postoperative day the animals were examined for respiratory excursion. The brain and spinal cord were prepared to show cells or myelin. Chromatolysis, chiefly ipsilateral, of many, but not all, of the cells of the inferior reticular nucleus was observed.

ADDISON, Philadelphia.

NERVE-MUSCLE SPECIFICITY IN AMBLYSTOMA, STUDIED BY MEANS OF HETEROTOPIC CORD GRAFTS. JEAN PIATT, J. Exper. Zool. **85**:211 (Nov.) 1940.

Portions of the spinal cord of embryos of Amblystoma punctatum were transplanted homeoplastically to a position equidistant from the forelimb region and the developing hypobranchial spinal musculature. Grafts from three different regions

of the cord were studied. In each series the isolated segments of cord differentiated and formed spinal ganglia, dorsal and ventral roots and nerves. The nerves from the grafted portion of the cord grew into forelimb and hypobranchial spinal muscles indiscriminately and impartially. Data from 178 animals showed that the two muscle fields received an approximately equal qualitative innervation in the three series. In many cases nerves from the grafted portion of the cord anastomosed with the vagus nerve or directly supplied vagus effectors. There was no evidence that this ectopic innervation was functional. The ectopic innervation of the forelimb muscles was shown to be functional and that of the hypobranchial muscles was probably functional, although not proved to be so. It is concluded that developing neurons in the spinal cord of Amblystoma have no inherent affinity for the muscles which they normally supply, but that all motor neurons are alike in their capacity to reach peripheral fields. The patterns of distribution in normal ontogenic development must be the result of extrinsic factors other than a specific attraction exerted by muscle groups.

WYMAN, Boston.

## Neuropathology

CEREBRAL COMPLICATIONS FOLLOWING SURGICAL OPERATIONS: II. FACTORS WHICH PREDISPOSE TO CEREBRAL ANOXIA. ALBERT BEHREND and HELENA E. RIGGS, Arch. Surg. **41**:772 (Sept.) 1940.

Behrend and Riggs have demonstrated that most types of postoperative cerebral complications may occur as a result of cerebral anoxia. In the cases studied anoxia was usually secondary to an acute general circulatory collapse precipitated by administration of an anesthetic plus the trauma of operation in patients whose margin of circulatory reserve had been reduced. In many cases the presence of such a preexisting chronic circulatory insufficiency was unsuspected either by the patient or by his physician, but histologic observations on the vital organs were interpreted as evidence of such a disturbance. While the cerebral changes appeared to be the result of anoxia operating through general circulatory insufficiency, it was evident that such anoxia could be produced by various mechanisms and that more than one mechanism could be present in a given case. There are four main types of anoxia. The first is stagnant anoxia, in which, because of slowing of the blood current, tissue asphyxia occurs. The second is anemic anoxia, which occurs when the hemoglobin content of the blood is too low to allow sufficient oxygen to be carried to the tissues. The third is histotoxic anoxia, which occurs when the cells are so damaged as to be unable to utilize oxygen. A common cause of this condition is the overenthusiastic use of morphine, barbiturates, anesthetic drugs or alcohol. The fourth is anoxic anoxia, which may occur throughout the body as a result of an insufficiency of the available supply of inspired oxygen or locally as the sequel of trauma, acute inflammation or gas gangrene. Among the factors important in determining a predisposition toward anoxia is organic heart disease. In 76 per cent of the cases studied post mortem by the authors an organic cardiocirculatory lesion existed prior to operation. Other factors listed as predisposing causes are anemia, age, metabolic disorders, vitamin deficiency, surgical emergencies, such as shock, hemorrhage and overwhelming infection, and the type of anesthesia used.

GRANT, Philadelphia.

CHANGES IN THE VASCULAR PATTERN OF THE BRAIN IN EXPERIMENTAL TRAUMA. M. HELFAND, Psychiatric Quart. **15**:33 (Jan.) 1941.

Helfand continues a previous study on the effects of trauma on the brain. In the earlier study significant changes were found in the brain which were attributed to vasomotor dysfunction, though frequently structural changes in blood vessels were not seen. In the present work the Lephene and Pickworth stain was used to show changes in the vascular patterns. Areas of relative anemia were observed in the brains of 5 control cats. The experimental series consisted

of 11 cats which received trauma to the vertex by the impact of a kilogram weight dropped from heights of 1½ to 3 feet (45 to 91 cm.). The effects of single and repeated traumas were studied at varying intervals after the injury. Disturbances in the vascular pattern were found, depending on the degree of injury sustained. In only 2 cases were there massive hemorrhages. Some vessels showed no stainable contents; others were distorted and showed variations in caliber, dilatation and engorgement, with or without diapedesis. The smaller vessels were affected chiefly. These variations were thought to be phases of physiologic disturbance and for the most part reversible if the injury was not too great. Ganglion cell changes were dependent, also, on the duration of the circulatory changes.

SIMON, Worcester, Mass.

A FORM OF FAMILIAL PRESENILE DEMENTIA WITH SPASTIC PARALYSIS. C. WORSTER-DROUGHT, J. G. GREENFIELD and W. H. MCMENERMEY, Brain **63**:237, 1941.

The authors report 11 cases of a familial form of presenile dementia, appearing in one family during three generations, with pathologic examination in 1 of them. Nine females and 2 males were affected.

The onset is usually in the fifth decade. It begins insidiously, with weakness and stiffness of the legs. Speech is affected early, and dysarthria may be the first symptom. Mental changes probably begin at the same time as the spasticity, but frequently are not recognized as soon. Personality changes are striking, with apathy, alternating with irritability, and general loss of initiative. There are failure of recent memory and progressive mental deterioration. The course is progressively downhill, leading to death in two to eleven years. In the later stages there is evidence of diffuse cerebral damage: nystagmus, amentia, incoordination and spastic paralysis.

Gross examination of the brain revealed shrinkage of the white matter of the cerebellum and cerebral hemispheres, with pronounced and uniform atrophy of the corpus callosum. The lateral ventricles showed some degree of dilatation.

Myelin stains revealed diffuse rarefaction of the white matter. Demyelination was especially severe in the corpus callosum, where many microglia phagocytes containing fat were present.

The cause of the demyelination appears to be an unusual change affecting the small arterioles of the pia mater and the white matter, and to a lesser extent those of the cerebral cortex. These vessels showed two main types of change. The first consisted of hyaline swelling of the middle coat, with loss of nuclei, and was observed chiefly in the small vessels of the pia, but also in those of the white matter, especially in relation to the partially demyelinated areas. The second type was seen only in relation to a small proportion of the vessels of the white matter and cortex. It consisted of a concentric or nodular zone from which the myelinated fibers had been pushed back by amorphous tissue, containing many fine neuroglial fibers.

Changes in the blood vessels of the cornu ammonis and cerebellar cortex were particularly marked. In addition, clear areas, varying in size from 12 to 100 microns, were seen both inside and just outside the fascia dentata. In silver preparations many of these could not be distinguished from senile plaques but others were more structureless. They consisted of a densely interwoven mass of very fine fibers, presumably of neuroglial origin. These interrupted the line of nerve cells in the fascia dentata. Smaller foci were numerous among the pyramidal cells of the cornu ammonis. Many of the latter showed Alzheimer's neurofibrillary cell changes. The molecular layer of the cerebellum showed similar changes.

The authors conclude that the degeneration of myelin is secondary to the vascular changes. The changes in the vessels and the plaquelike structures are closely related, but the primary process and the cause of changes in the vessels have not been determined.

MASLAND, Philadelphia.

A Brain After Supposedly Complete Operative Removal of a Glioma. B. Brouwer, Monatschr. f. Psychiat. u. Neurol. **102**:193, 1940.

Brouwer studied a case of cerebral glioma in which complete removal of the tumor had supposedly been accomplished. The histologic diagnosis was fibrillary astrocytoma. Convalescence was satisfactory, but six weeks after the operation sudden death from pulmonary embolus occurred. Gross inspection of the brain failed to disclose any evidence of remaining tumor tissue; yet on microscopic examination several collections of gliomatous cells were observed in the parts surrounding the excised area. Apparently, it is not always possible to determine the exact limits of a new growth by ordinary inspection and palpation. Brouwer suggests that frozen sections obtained from the margins of the operative field should be examined while the operation is still in progress, in order to decide whether sufficient tissue has been removed. In this way the prospects of avoiding recurrences should be increased.

Rothschild, Foxborough, Mass.

## Psychiatry and Psychopathology

Psychoses Resembling Schizophrenia Occurring with Emotional Stress and Ending in Recovery. Harry A. Paskind and Meyer Brown, Am. J. Psychiat. **96**:1379, 1940.

Paskind and Brown report 5 cases of a psychosis characterized by a rapid onset following incarceration. The clinical picture consisted of attention defect, hallucinosis, impaired orientation, memory defect (apparent if not real), impairment in judgment, delusions, flattening of affect and impairment of volition and self expression. The authors point out the similarities to schizophrenia but differentiate the condition on the basis of rapid onset following emotional upset, constancy of recovery, disorientation and frequency of amnesia.

Paskind and Brown conclude that the similarity to schizophrenia is pronounced because the same mechanisms are involved in the two conditions. The scarcity of reports of this psychosis in civil life may be due to the inclusion of such cases under schizophrenia.

Forster, New Haven, Conn.

A Study of One Hundred Patients Suffering from Psychosis with Cerebral Arteriosclerosis. Hollis E. Clow, Am. J. Psychiat. **97**:16, 1940.

Clow studied the histories of 100 patients admitted to the hospital during twenty-two and one-half years because of psychosis associated with cerebral arteriosclerosis. The group comprised 55 men and 45 females; 76 were married or had formerly been married; all were well educated, were normally intelligent and had for the most part been successful. The median age of the group was 64. The frequency of a family history of cardiovascular-renal disease was high, and the families, like the patients, tended to have tense, aggressive personalities. Manic-depressive episodes had been frequent among the patients prior to the present illness. The onset of the illness was usually gradual, and extraneous factors played a part in precipitating the psychosis in 45 cases. Emotional factors seemed of greatest importance. The most common clinical picture was that of delirium. Treatment consisted of psychotherapy combined with suitable symptomatic measures aimed at the physical status. Sixty-four per cent of the patients improved, and 11 recovered. Clow concludes that the prognosis is better in the presence of a definite external precipitating factor.

Forster, New Haven, Conn.

Prognosis of Hebephrenia. B. S. Gottlieb, Psychiatric Quart. **15**:54 (Jan.) 1941.

Gottlieb attempts to determine the prognostic value of various clinical features of hebephrenic schizophrenia in an analysis of 100 cases. No particular symptoms appeared to have special significance. Approximately 50 per cent of the patients

with an acute atypical onset improved or recovered, as against 20 per cent of those with an insidious typical onset. The atypical onset is characterized by much confusion and often depression at the beginning and before the establishment of the characteristic symptoms. The author finds it useful to divide the disorder into the prodromal, the acute, the stationary and the chronic phase. In agreement with Kraepelin's view, he considers the early manifestations of hebephrenia to be a prodromal phase of hebephrenia rather than evidence of a preschizoid personality type.

SIMON, Worcester, Mass.

PSYCHOSIS WITH HUNTINGTON'S CHOREA. D. ROSENBAUM, Psychiatric Quart. **15**:93 (Jan.) 1941.

Rosenbaum studied the mental symptoms of 46 patients with Huntington's chorea. The average age of onset of the psychosis and chorea was 46 and 45, respectively. All but 6 of the patients had died or were still hospitalized. The average age at death was 54, and that of the patients still in the hospital, 57. The commonest, and frequently the most prominent, psychiatric symptom was emotional instability, chiefly irritability, which was present in 41 patients. Frank deterioration was found in 35 patients; in 42 defects in memory, mental tension and attention appeared. Less deterioration was found early in the disease. Delusions, mostly paranoid, unsystematized delusions against family or friends, were present in 38 patients. A smaller number displayed grandiose ideas. Over half the patients were hallucinated. None had convulsions. About one-third showed depression, and a history of suicide in afflicted members of the family was frequently noted.

SIMON, Worcester, Mass.

UTILIZATION OF EARLY CURRENT DREAMS IN FORMULATING PSYCHOANALYTIC CASES. LEON SAUL, Psychoanalyt. Quart. **9**:453, 1940.

From a study of a number of cases Saul reiterates the concept that the first ten or fifteen dreams during a psychoanalysis, if carefully studied, give the essential facts in the whole case. In the study of these early dreams attention should be directed especially to (1) the tendencies readily apparent and the manifest content in the light of the history, life situation and associations; (2) the part played by the dreamer in his own person in the manifest content, a valuable clue to the kind and degree of repression and the status of the ego; (3) the status of the conflict, especially the kind and degree of the solution and the amount of regression and gratification, and (4) if necessary for special studies, the balance between intaking and eliminating tendencies and the status of the hostilities.

Saul cites several series of early dreams and relates their interpretation to the patient's life situation and history. He points out that this method is particularly valuable in formulating the psychopathologic factors in cases of psychosomatic disorders. As an illustration of this, he cites 4 cases of essential hypertension in men whose dreams showed a striking similarity of the nuclear conflict and its status. All 4 patients, when the blood pressure was at its peak, had dreams of being caught by a man in a sexual situation with a woman with no adequate means of escape or other solutions represented. When the blood pressure was low the dreams ended in escape or regression.

PEARSON, Philadelphia.

FOUR TYPES OF NEUROTIC INDECISIVENESS. EDMUND BERGLER, Psychoanalyt. Quart. **9**:481, 1940.

Indecision is the final outcome of a conflict between an unconscious desire and an unconscious punishment for the desire. In his analytic work, Bergler has found four types in which the symptoms were the same but the underlying conflicts were different, and he believes that there are probably several more varieties. He has defined these types as follows: Type 1: Indecision resulting from the acting out of a magical gesture. In the case which Bergler cites, the patient's apparent extrav-

agence resulted from inability to discriminate about what he wished to buy. This was a magical gesture which indicated the way in which he wished his mother to treat him, i. e., that she should not discriminate against him. It served also as a reproach that because she had discriminated wrongly in her fondness for her children he could not learn to discriminate in buying.

Type 2: Indecision as a result of the withdrawal of an unconscious prop for feelings of guilt. Some neurotic persons can get along if they displace their infantile wishes and suffer unconscious punishment for them. If this pattern is interfered with their feelings of guilt make them indecisive.

Type 3: Indecision associated with retrospective enthusiasm. The illustrative case is that of a masochistic man who in the presence of a man to whom he was attached appeared indifferent and indecisive. At the same time he was enthusiastic about another man. In the presence of the second, however, he behaved again as he did with the first.

Type 4: Pseudoindecision in oral neuroses. Bergler points out that the behavior of a neurotic person with an oral regression is not that of "I want something" but of "I refuse something I want in order to take revenge." This behavior results in an attitude closely resembling indecision. PEARSON, Philadelphia.

AGGRESSION IN THE RESCUE FANTASY. RICHARD STERBA, Psychoanalyt. Quart. **9**:505, 1940.

The rescue fantasy is often regarded as a life-preserving, love-offering attitude by the person having the fantasy. This is particularly so when the son has a rescue fantasy about the mother. Here he wishes to give back to her the life he owes her by rescuing her from the danger of death. Sterba gives several examples of female patients in whom a hostile, aggressive attitude was expressed by the rescue fantasy in which the analyst was in danger, which was undone by the element of rescue.

PEARSON, Philadelphia.

ACUTE WAR NEUROSES. W. SARGANT and E. SLATER, Lancet **2**:1 (July 6) 1940.

According to Sargant and Slater, cases of acute war neuroses, such as arose in the Flanders retreat, demonstrated that men of reasonably sound personality may break down if the strain is severe enough. This does not deny the importance of constitutional factors. Compared with an average population, this group of men would almost certainly show an excessive proportion who had suffered from nervous troubles in earlier life and an excessive frequency of psychiatric disorders in the blood relatives. Nevertheless these men had shown a satisfactory adaptation to army life, and the previous history showed in most cases a man of normal intelligence, personality and work record. The stress required to produce a breakdown of such personalities was of an altogether different order from any to which they could expect to be subjected in ordinary life. It was an accumulation of strains, both physical and mental, of great intensity. The clinical picture was surprisingly uniform. There were the signs of physical exhaustion: thin, fallen-in face, pallid or sallow complexion. The expression and the whole attitude of the body were those either of tension and anxiety or of listless apathy. Neurologic signs of a functional nature were usually present. A coarse, irregular tremor of the hands was common. The resemblance to a parkinsonian picture was often increased by an immobile facies, and the superficial resemblance was so great that in a number of cases a diagnosis of parkinsonism had been made. Reflexes were usually exaggerated, occasionally sluggish. Mentally the patients complained of the usual symptoms of the acute anxiety state: sleeplessness, terrifying bad dreams, a feeling of inner unrest and a tendency to be startled at the least noise, but particularly at the sound of an airplane going overhead or any sound resembling it. The course taken by these patients under treatment was uniformly toward improvement. The change in appearance in the first few days with adequate sleep, rest and food was striking. Tremors rapidly diminished in intensity, as did also the general attitude of tension. The degree to which recovery is complete is more

doubtful. It seems that these patients have gone through a process for which the term conditioning may be used. The first essential of treatment is to secure rest. This may be done in cases of the milder neuroses by confinement to bed for a few days and the administration of an effective hypnotic. This must be combined with a full diet and ample fluids. The best method of securing the essential sleep varies with different patients. For some a quickly acting drug with an effect that lasts only a few hours may be all that is necessary. But the majority find difficulty not so much in getting to sleep as in remaining asleep. For these a drug with a longer effective action will be required. A considerable number of the more severely affected will require a course of continuous narcosis. It will get them through the worst period of their convalescence without their being aware of the severity of their symptoms, and it helps to minimize the process of conditioning. Any of the standard methods of narcosis may be employed. The Mira method, employed in the Spanish civil war, has been found disappointing in some cases, since the narcosis was not always complete. As a rule, continuous narcosis has not been given for much longer than a week. It was found desirable to relieve acute hysterical symptoms, including amnesias, at the earliest moment by persuasion during hypnosis, produced directly or with the aid of intravenous injection of barbiturates.

J. A. M. A.

ANALYSIS OF ONE HUNDRED CASES IN A SPECIAL PSYCHIATRIC SERVICE FOR ALCOHOLIC PATIENTS IN THE PARIS AREA. J. DUBLINEAU and H. DUCHENE, Encéphale **2**:275 (June) 1940.

Dublineau and Duchene studied 100 consecutive patients admitted to a service for alcoholic patients during the winter of 1938-1939. Of these, 36 were classified as chronic heavy drinkers, 31 were moderate drinkers and 33 were not alcoholic, though so certified. Half the patients came from the courts and the rest from hospitals. Antisocial acts symptomatic of character defects occasioned the admission of 69 per cent of the heavy drinkers, and confusional states, only 19 per cent. Among the moderate drinkers mental confusion was the largest single cause for admission (45 per cent). Hallucinatory delirium was the chief reason for admission of nondrinkers (42 per cent). Psychotic symptoms of the heavy drinkers usually cleared. The moderate drinkers did poorly in the hospital, 77 per cent remaining unimproved. In these the confusion was an introductory phase in a continuing "process" psychosis. The prognosis for the nondrinkers was also that of the underlying psychosis.

Alcoholism was six times as frequent among parents of heavy drinkers, and three times as many of their siblings and twice as many of their children died early as did those of the moderate drinkers and nondrinkers. The histories of heavy drinkers showed increased unemployment, delinquency, previous commitments, cerebral trauma (frequently associated with arterial hypertension) and infection with malaria and syphilis. Examination of the heavy drinkers showed 41 per cent with pupillary abnormalities, 50 per cent with persistent arterial hypertension, 12 per cent with polyneuritis and 6 per cent with hepatic disease. The incidence of convulsions was twice as high (20 per cent) among the moderate drinkers.

HOLT, Worcester, Mass.

THREE CASES OF KLEPTOMANIA. H. GRELINGER, J. belge de neurol. et de psychiat. **40**:105 (March) 1940.

Grelinger reports instances of kleptomania in boys aged 16 and 17 and a woman aged 53. In each case there was a definite correlation between the act of stealing and onanism. Oral sadism was marked in all 3 cases. In the boys there was a tendency toward exhibitionism.

DE JONG, Ann Arbor, Mich.

PSYCHIC SYMPTOMS IN NEUROSURGICAL DISEASE. E. BUSCHE, Acta psychiat. et neurol. **15**:257, 1940.

Busche reports the results of a review of a large series of records of patients with many sorts of intracranial neurosurgical diseases. No detailed psychiatric studies had been made. Increased intracranial pressure was associated only with stupor and eventually with loss of consciousness. Nonstuporous patients with high intracranial pressures showed no intellectual or memory loss. Moria appeared to be most common with tumors of the frontal lobes, while dementia was seen in cases of tumors involving extensively the hemispheres and basal structures. The well known disturbances of consciousness associated with tumors of the third ventricle were also noted. In the opinion of the author, there are no special psychic symptoms to be found with tumors of the corpus callosum unless these tumors have extensively encroached on the neighboring hemispheres, and it is stated that a number of the author's patients who have survived operations involving section of large parts of the corpus callosum have shown no residual psychic defects. The author feels that there would be great profit in an intensive and expert psychiatric review of neurosurgical patients before and after operation.

BRENNER, Boston.

## Diseases of the Brain

PROGNOSTIC CRITERIA IN DEMENTIA PARALYTICA. MAURICE H. GREENHILL and MORRIS YORSHIS, Am. J. Psychiat. **97**:167, 1940.

Greenhill and Yorshis studied 100 patients with dementia paralytica treated by malaria, standard diathermy, modified diathermy or tryparsamide alone. Malaria therapy gave the best results. The following features were found to be of prognostic importance: (1) duration of illness of less than one and a half years was of good import; (2) previous therapy augured well for a favorable outcome; (3) the presence of neurologic impairment indicated a poor prognosis; (4) convulsions and deterioration augured poorly for recovery, and (5) the type of dementia paralytica and (6) evidence of spontaneous remission were of significance. The personality prior to the illness was found to be of marked importance, the patients who made a poor adjustment before the onset having a poor prognosis. The degree of the maladjustment was found to be in direct correlation with the severity of the symptoms. Greenhill and Yorshis point out the importance of including all these prognostic criteria in the evaluation of each case.

FORSTER, New Haven, Conn.

CEREBRAL ABSCESS (PARADOXIC) ACCOMPANYING CONGENITAL HEART DISEASE. I. S. WECHSLER and ABRAHAM KAPLAN, Arch. Int. Med. **66**:1282 (Dec.) 1940.

Cerebral abscess occasionally is a manifestation of congenital heart disease. The abscess generally is single, is in the right cerebral hemisphere and occurs most frequently in cases in which the signs point to the tetralogy of Fallot. Twelve cases had previously been reported; to these the authors add 2 of their own. These 2 cases and 1 other were the only instances in which the condition was recognized during life; in the others the anomaly was not even suspected. It usually was thought to be either cerebral embolism or thrombosis. Such a conclusion is justified to some degree by the rapidity of the abscess formation, but the presence of fever, leukocytosis, slow pulse and early modification of the fundus suggests an infectious, expanding intracranial lesion. It is important, therefore, to recognize that cerebral abscess may occur in persons with congenital heart disease even though a primary focus of infection cannot be found. There is no adequate explanation of the mechanism of the production of "paradoxic" cerebral abscess. It has been stated that this condition can occur when there is a defect in the ventricular system and dextraposition of the aorta. This combination seems

to favor a direct path for the transmission of a crossed embolus. Another possible explanation is that vascular disease of the brain, with consequent encephalomalacia, prepares a focus which is receptive to infection.

Previously most of the emphasis in these cases has been placed on the valvular and vascular defects, with altogether too little attention focused on the cerebral complications. Surgical intervention directed toward the latter may lead to recovery.

BECK, Buffalo.

PROLONGED COMA AFTER INSULIN HYPOGLYCEMIA. DOUGLAS GOLDMAN, J. Nerv. & Ment. Dis. **92**:157 (Aug.) 1940.

Goldman observed prolonged posthypoglycemic coma on 23 occasions during the giving of 5,882 insulin shock treatments to 108 patients. He found the condition clinically distinct from the preceding hypoglycemic shock and characterized by (1) the persistence of coma after the level of blood sugar had returned to normal, (2) hyperventilation, leading often to tetany, with motor excitement, rigidity and typical spasm, and (3) fever, proportional to the muscular exertion. In addition, the skin was dry and often cyanotic or locally hyperemic, the Babinski reaction was absent and the corneal and pupillary reflexes were weak or abolished, even with marked motor excitement. The febrile period lasted usually six to eighteen hours and was followed by diminishing stupor for ten to fifteen hours, but confusion sometimes lasted for weeks. Deep and prolonged hypoglycemic shock seemed to be the only predisposing cause.

Chemically, the hyperventilation produced alkalosis, while loss of fluids led to concentration of the blood and relative loss of chlorides. Bronzing of the skin in 1 patient also suggested that there was an acute adrenal cortical deficiency. Treatment with intravenous injection of physiologic solution of sodium chloride up to 1,200 cc. combined with administration of 3 to 10 cc. of adrenal cortex extract, if begun within one hour, usually relieved the motor excitement and hyperventilation in twenty minutes. After one to three hours sweating recurred and the level of the blood sugar fell. Since the introduction of this treatment, no prolonged stupors had occurred in 17 cases of posthypoglycemic coma.

MACKAY, Chicago.

ALZHEIMER'S DISEASE. A. FERRARO and G. A. JERVIS, Psychiatric Quart. **15**:3 (Jan.) 1941.

Ferraro and Jervis reported 2 cases of Alzheimer's disease developing in the fourth decade. In both, the characteristic clinical features of progressive mental deterioration and focal cortical and neurologic signs were present and the characteristic pathologic changes were observed at autopsy. These cases, with 5 similar cases from the literature, are discussed, and it is suggested that the term "adult type" of Alzheimer's disease be used to designate the form with onset before the presenium, between the ages of 25 and 40. Whether there is a "juvenile" type is considered doubtful.

SIMON, Worcester, Mass.

MANAGEMENT OF CEREBRAL GLIOMAS. G. PHILLIPS, M. J. Australia **2**:301 (Oct. 5) 1940.

Phillips reports 2 deaths in hospitals in a series of 35 consecutive cases of cerebral or cerebellar tumors removed surgically. One death occurred eight weeks after operation as a result of an accident, while the other occurred fourteen days after operation as the result of intracranial hemorrhage. Twenty-eight of the 35 operations were performed in the presence of a large space-occupying lesion in the skull, associated in each instance with a considerable increase of intracranial pressure; 1 patient died as the result of late wound infection. The results substantiate the claim that with adequate management cerebral tumors may be exposed and removed with a relatively low surgical mortality rate. Operation with local anesthesia makes this possible. The patient's ability to complain of

pain, cold and discomfort and the opportunity to provide adequate fluid by mouth during prolonged surgical procedures are constant guardians against cerebral shock. Except with children, the author rarely uses general anesthesia. Twenty-two of the intracranial tumors were gliomas. The whole tumor was removed in 10 cases and the greater part of the tumor in 8; in 4 cases, for various reasons, no attempt was made to remove the tumor, which after exposure was treated with high voltage roentgen radiation. The author believes that, irrespective of the skill of the surgeon, operations for cerebral glioma will frequently be succeeded by a fatality if these tumors are considered as a single group and submitted to an indiscriminate surgical procedure. Particularly is this so since nearly 40 per cent are glioblastomas. A major responsibility for the surgeon is to equip himself with information concerning the frequency, location and full life history of cerebral gliomas. The capacity for diagnosing cerebral gliomas preoperatively is almost the *sine qua non* of continued success. The pertinent facts are summarized. The percentages for the different types of gliomas are: glioblastomas 40, astrocytomes 40, medulloblastomas 12, oligodendrogliomas 2, ependymomas 2 and all the rare types 4. The average postoperative period of survival for the respective tumors is twelve months, from six to ten years, from two to four years, more than six years and six to ten years; for the rare types the survival time is variable. The average age at which glioblastomas occur is between 40 and 60; for astrocytomas of the cerebrum it is 30 and for those of the cerebellum 13; the average age for medulloblastomas is 10 and for oligodendrogliomas 30; the ependymomas and the rare types occur at various ages.

J. A. M. A.

Importance of Trauma to the Skull for Development of Organic Cerebral Changes. H.-H. Meyer, Deutsche med. Wchnschr. **66**:316 (March 22) 1940.

According to Meyer, the importance for the brain of trauma of the skull has received greater attention in recent years because of the increase in traffic accidents. He reports 2 cases, in both of which the skull trauma seemed to be of a harmless nature. There had been no injury to the bones of the skull, nor had there been loss of consciousness or vomiting. Acute exacerbation developed after four and thirty-one days, respectively, probably as the result of a hemorrhage. In 1 patient hemiplegia and speech disturbance developed, and in the other, symptoms of pressure on the brain and epileptiform attacks. These cases demonstrate that the lack of symptoms immediately after the trauma does not prove that the brain has escaped injury. The interval between the trauma and the appearance of severe cerebral symptoms may vary greatly. There have been cases of skull trauma in which epileptiform attacks, jacksonian seizures and metabolic disturbances developed years later. Encephalographic examination is an important aid in many cases. The displacement and widening of the ventricles and differences in the visualized subarachnoid space permit important conclusions. It may be assumed that such changes are partly due to tissue destruction, to shrinkage of the tissues or to glial scars and tensions produced by cicatrices. Great care is necessary in the estimation of encephalographic pictures, because not all changes have a traumatic origin. If these are observed in cases in which the history reveals a cranial trauma, one is justified in ascribing them to this trauma.

J. A. M. A.

## Diseases of the Spinal Cord

Transverse Diffuse Myelitis of the Spinal Cord Following Intravenous Neoarsphenamine. Vince Moseley and J. Lamar Gallaway, Am. J. Syph., Gonor. & Ven. Dis. **24**:746 (Nov.) 1940.

Moseley and Gallaway report the case of a woman aged 24 in which transverse myelitis occurred after the second intravenous injection of neoarsphenamine. The dose was not known, but was said to have been larger than was intended. After both injections the patient experienced immediate visceral symptoms, which soon

abated. Other investigators have expressed the opinion that the myelitis results from a delayed type of toxic reaction to neoarsphenamine. The authors, however, believe that the injury to the spinal cord occurred as a result of a Jarisch-Herxheimer reaction in a patient suffering from syphilis of the central nervous system with focal parenchymatous lesions in the brain and spinal cord.

The Jarisch-Herxheimer reaction is compared with the reaction which occurs in patients with tuberculosis in whom there exists an allergic sensitivity to the tubercle bacillus or its products. If the tubercle bacillus or some part of this organism is injected, both an acute inflammatory response takes place at the sites of the tuberculous infection and a generalized systemic reaction of fever and malaise occurs. In syphilis a similar type of inflammatory response seems to occur at the sites of spirochetal infection if the protein or other portion of the spirochete is suddenly released into the general circulation. The spirochetal allergens are released in some manner after destruction of large numbers of the organisms from the rapidly acting spirocheticidal arsenical. In early syphilis the usual Jarisch-Herxheimer reaction consists of fever, chill, malaise and an increase in cutaneous manifestations. In late syphilis there are not only systemic manifestations but also acute inflammatory responses at focal areas of infection. In this manner a low grade infection of the cardiovascular or central nervous system may suddenly be transformed into an acute inflammatory reaction with subsequent severe and often irreparable damage, as in the case reported. This serious complication of the treatment of late syphilis can be prevented by preliminary treatment with iodides and heavy metals for four to six weeks before the administration of arsenical products.

BECK, Buffalo.

CRANIAL CHORDOMAS. W. JAMES GARDNER and OSCAR TURNER, Arch. Surg. **42**:411 (Feb.) 1941.

The term chordoma refers to a neoplasm arising from embryonic rests of the chorda dorsalis, or notochord, which in its development more or less reproduces the structure of the primitive notochord. Chordomas arise in the craniospinal axis in certain definite locations, the selection of which can be explained on an embryologic basis. While they rarely metastasize, the clinical course is characterized by slow expansile enlargement, with destruction of adjacent bone and compression of neural structures, and by recurrences after operation.

The invasive and malignant growths are often large, compressing the adjacent neural tissue, enveloping nerves and invading and destroying the contiguous bony structures. The tissue is poorly vascularized, but the tumor is apt to have a reddish brown color, due to interstitial hemorrhage. The well circumscribed appearance of the growth belies the microscopic appearance and clinical behavior.

The most common intracranial location is at the spheno-occipital synchondrosis. Originating from the clivus, these tumors are essentially in the midline at first but extend widely in all directions. They may be associated with a variable degree of destruction of the basilar process of the occipital bone. On the roentgenogram this may be revealed as a V-shaped notch in the basilar plate, or it may be represented by evidence of destruction of bone. Anterior extension may be sufficient to involve the parasellar structures. Occasional cases have been reported in which there was extension into the anterior fossa. Ventrally, the growth of the tumor may be sufficient to involve the nasopharynx, maxillary sinus and posterior choanae. The primary involvement is of the pons and medulla, where lesions may produce the characteristic cranial nerve palsies, with severe clinical symptoms. Occasional cases have been recorded in which the growth arose from the body of the sphenoid bone. Tumors arising from the anterior extension of the chorda encroach on the sella and suprasellar structures and simulate the usual tumors arising in this region.

The first of the 3 cases described was that of a woman aged 35 who had had symptoms for two years. The second, third, fourth and sixth nerves were

involved; the visual fields showed hemianopia; roentgenograms revealed calcification in a tumor of the temporal lobe and erosion of the left sphenoid ridge. Operation revealed an entirely extradural tumor which filled the left middle fossa with an extension about 2 cm. in width crossing the tip of the petrous bone to a point of attachment on the posterior surface of the basilar bone. The gelatinous material could be easily removed from the shell of the tumor, and almost all the capsule could be extirpated. Convalescence was satisfactory. Thirteen months later the involvement of the cranial nerves was rapidly improving.

The second case was that of a woman of 35 who had had her symptoms for about six months. All the cranial nerves on the left side except the olfactory and optic were involved. Left hemiparesis was present. The preoperative diagnosis was that of a tumor of the cerebellopontile angle. Suboccipital craniectomy revealed a smooth, round, bluish, encapsulated tumor beneath the pons, across which were stretched the seventh, eighth, ninth, tenth and eleventh nerves. Incision into the capsule revealed a semisolid, translucent material, which could be readily sucked out. All the capsule could be removed except for the point of its attachment to the basilar bone. The patient made a rapid postoperative recovery, with marked return of function.

The third case was that of a woman of 22 who had had symptoms for two years. The cranial nerves from the fifth to the twelfth were involved. There was a decided bulge on the right side of the nasopharynx. Right cerebellar craniotomy exposed a smoothly encapsulated tumor, apparently originating from the basilar bone anterior and medial to the jugular foramen. The ninth, tenth and eleventh nerves were stretched over the growth. The capsule was incised and the pinkish, soft mucoid contents removed by suction. The tumor had eroded through the basis cerebri, and the capsule could not be removed at this point. Operative recovery occurred, with some improvement, but the patient died ten months later from recurrence.

These tumors, since they are well encapsulated and contain material which can be rapidly removed, offer a fair prognosis. The diagnosis is suggested by multiple cranial nerve palsies when associated with evidence of a lesion in the middle fossa. The diagnosis is even more likely when air studies indicate upward displacement of the third ventricle, the aqueduct of Sylvius and the fourth ventricle. The basilar plate may be characteristically notched in the roentgenogram.

GRANT, Philadelphia.

## Vegetative and Endocrine Systems

QUANTITATIVE SEX HORMONE STUDIES IN HOMOSEXUALITY, CHILDHOOD AND VARIOUS NEUROPSYCHIATRIC DISTURBANCES. RALPH NEUSTADT and ABRAHAM MYERSON, Am. J. Psychiat. **97**:524, 1940.

Neustadt and Myerson report the results of 600 colorimetric urnialyses for androgens and estrogens in 200 subjects. They first determined the normal curve for daily androgenic excretion and the relation of androgen to estrogen. Twenty-five of 29 overt homosexual persons showed an increase in estrogens and a relative decrease in androgens. Among patients impotent on the basis of minor neuroses low excretions of both androgens and estrogens were found. The majority of masturbators were found to have an increase in both androgens and estrogens. In female castrates both androgenic and estrogenic substances were very low. A man with eunuchism of twenty-five-years' duration still excreted a considerable, but less than normal, amount of androgen. Excretion is high with adrenal tumors and low with disease of the pituitary. Observations on the major psychoses are still incomplete, but no relationship could be found between endocrine excretion and involutional melancholia.

FORSTER, New Haven, Conn.

Effects of Hypophysial Stalk Resection on the Hypophysis and Hypothalamus of Man. A. T. Rasmussen and W. J. Gardner, Endocrinology **27**:219 (Aug.) 1940.

Rasmussen and Gardner studied the hypophysis and hypothalamus in a man aged 47 with malignant hypertension five months after almost complete surgical interruption of the nerve fibers in the infundibulum and two weeks after a unilateral cerebral hemorrhage.

Histologic examination of the region of operation revealed typical cellular condensation and atrophy of the processus infundibuli, but the pars intermedia was not appreciably changed. The resection of the stalk by electrocauterization had resulted in the fibrosis and reduction of the normal parenchyma of the anterior lobe to about two fifths of the average normal amount. The loss of 85 per cent of the cells of the supraoptic nuclei was interpreted as a simple retrograde degeneration resulting from cutting their processes in the infundibular stem. In spite of this large diminution in the supraopticohypophysial region and alterations in the neurohypophysis, no diabetes insipidus resulted in the five months following the operation. While the hypertension decreased after the resection of the hypophysial stalk, the effects on the blood pressure of the decompression, together with the early death of the patient, prevent the drawing of any conclusions on the significance of the reduction of blood pressure by this procedure.

Palmer, Philadelphia.

The Effect of Adrenalectomy on the Anterior Pituitary of Fowls. E. H. Herrick and J. C. Finerty, Endocrinology **27**:279 (Aug.) 1940.

The results of adrenalectomy in 10 adult male fowls were substantially the same as those described by other investigators; the testes in all cases became much reduced in size, and the external appearance of the birds suggested that of capons. The weights of all birds indicated that degeneration of the testes was not due to malnutrition. A detailed study of the pituitaries of these fowls indicated that the number of degenerating basophilic cells was approximately three times as great as that in normal fowls of similar age. The pituitaries of castrate fowls of similar age revealed a few degenerating basophils and an abundance of large basophils typical of the castrate type. It is believed that in adrenalectomized fowls the altered condition of the pituitary is the cause, not the result, of the degeneration of the testes.

Palmer, Philadelphia.

The Sugar Utilization of Hypophysectomized Rabbits. P. O. Greeley, Endocrinology **27**:317 (Aug.) 1940.

A study of the utilization of dextrose by the hypophysectomized rabbit shows marked differences and variations from that of the dog, rat and cat under the same conditions. The tissues of the rabbit seem to be adapted naturally to a higher level of dextrose consumption than are those of the cat, dog and rat.

The effect of hepatectomy on the dextrose consumption of the hypophysectomized rabbits was studied in an effort to determine whether or not the liver was rapidly converting the dextrose to fat. At the same time another group of rabbits was carried through in the same manner except that evisceration was substituted for hepatectomy. From the results obtained it is apparent that the removal of the liver and other abdominal organs does not change the dextrose requirements of the animal. It is concluded, therefore, that the general tissues of the hypophysectomized rabbits oxidize amounts of dextrose frequently as high as 700 mg. per kilogram of body weight per hour.

Palmer, Philadelphia.

Coexistence of Diabetes Mellitus and Diabetes Insipidus. P. A. Gray and W. M. Moffat, Endocrinology **27**:430 (Sept.) 1940.

Gray and Moffat report the coexistence of diabetes mellitus and diabetes insipidus in a man aged 53.

The diabetes mellitus, the presence of which was confirmed by a dextrose tolerance test, was controlled by diet and protamine zinc insulin. The diabetes insipidus was controlled equally well for a time by either the parenteral administration of solution of posterior pituitary U. S. P. or the nasal insufflation of posterior pituitary powder. However, the patient became allergic to both substances after two months and refused to continue their use.

Five months after the patient's discharge from the hospital, he was readmitted to the surgical service with a ruptured appendix, as a result of which he died. Examination of the pancreas disclosed pathologic changes compatible with those described as characteristic of diabetes mellitus. Pathologic changes in the pituitary gland were limited to the pars intermedia and pars neuralis and conformed to those found in diabetes insipidus. As the lesions in the pancreas and those in the pituitary gland were characteristic of entirely separate entities, it is probable that the coexistence of the two diseases was accidental. PALMER, Philadelphia

THE EFFECT OF FRESH AND EXPERIMENTALLY MODIFIED ANTERIOR HYPOPHYSIS OF CATTLE ON MITOTIC ACTIVITY IN THE ADRENAL CORTEX OF THE GUINEA PIG. H. T. BLUMENTHAL, Endocrinology **27**:486 (Sept.) 1940.

Implantation of fresh anterior hypophysial lobes of cattle into immature female guinea pigs causes an increase in the number of mitoses in the adrenal cortex of these animals. A similar effect is obtained by injections of an acid extract of the anterior lobes. An increase in mitotic activity, but to a lesser degree, is also obtained after implantation of cattle hypophysis which has been previously immersed in solutions of 95 per cent alcohol, acetone, glycerin or 50 per cent urea before implantation. Similar results are obtained from immersion of the gland in a combined solution of urea and glycerin before implantation. However, when the fresh glands were first treated with urea and then with alcohol or vice versa, the mitotic counts in the adrenal cortex were not at all raised, or only slightly, above those found in normal guinea pigs. A 50 per cent solution of urea has been shown to extract the active substance of the fresh gland, as evidenced by the decreased mitotic activity following implantation of the gland tissue so treated, but this extractive action can be diminished or prevented by first treating the gland with acetone or saturated ammonium sulfate before immersing it in a 50 per cent solution of urea.

The mitotic activity in the cortex of the adrenal gland seems to be a much more sensitive indicator for the determination of the effect of certain hormones than the change in weight which takes place in the gland under the influence of various agents. PALMER, Philadelphia.

RELATION OF CERVICAL SYMPATHETIC NERVES TO ACTIVITY OF THE THYROID. S. BROCK, G. E. DOTY, L. KRASNO and A. C. IVY, Endocrinology **27**:504 (Sept.) 1940.

In a series of 8 rabbits, the heat production of which had been determined before operation by the oxygen consumption method, the distal end of the cervical portion of the sympathetic trunk was stimulated after the method of Haney. An increase in basal metabolic rate was observed in only 1 of the 8 rabbits.

In 10 rabbits and 2 cats the cervical portion of the sympathetic trunk was removed from the stellate to the superior cervical ganglion, including as much of the former ganglion as possible. In 7 of the 9 rabbits studied longer than thirty days the metabolic rate was reduced from 10 to 30 per cent below the preoperative control level. The metabolic rates were decreased by 20 and 35 per cent, respectively, in the 2 cats. A control series of 2 rabbits submitted to a mock operation showed a uniform metabolic rate for four months or longer.

The authors conclude that bilateral cervical sympathectomy in rabbits causes fairly uniformly a decrease in the metabolic rate. PALMER, Philadelphia.

THE EFFECT OF PITUITARY STALK SECTION UPON REPRODUCTIVE PHENOMENA IN THE FEMALE RAT. E. W. DEMPSEY and U. U. UOTILA, Endocrinology **27**:573 (Oct.) 1940.

Dempsey and Uotila sectioned the pituitary stalk of 27 female albino rats by the parapharyngeal approach and observed the effect of the operation on the basic rhythm of the reproduction cycle, ovulation, mating, pregnancy and lactation. Studies were also made of the effect of prolonged exposure to cold on the reproductive cycle in animals in which the stalk had been cut and in control animals on which no operation had been performed.

The results obtained demonstrate that the basic rhythm of the reproductive cycle, ovulation, mating, pregnancy and lactation are normal after section of the pituitary stalk in the rat. Moreover, the reproductive cycle may proceed normally after section of the stalk despite exposure to cold for long periods, although cold lengthens the cycle and delays ovulation in control animals with the stalks intact.

These observations may be explained by the assumption that the rate of production of the gonadotropic hormones of the pituitary is modified by nervous influences. Removal of the nerve pathway by section of the stalk abolishes the modifying factors. The observations lend further support to the suggestion of Uotila that the pituitary stalk pathway subserves emergency functions and that the mechanism acts through the modification of the rate of production of the thyrotropic and gonadotropic principles in response to certain emergency situations.

Hypophysial deficiency sometimes occurs after section of the pituitary stalk and appears to be the result of inadvertent damage to the anterior lobe of the pituitary or to interference with its blood supply. Activation of the deficient anterior lobe in such cases sometimes follows the injection of extracts of the urine of pregnant women.

PALMER, Philadelphia.

OVARIAN INSUFFICIENCY IN MOTHERS OF MONGOLIAN IDIOTS. HEIN SCHRÖDER, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:148 (Aug.) 1940.

Schröder was interested in checking the findings of Geyer, who, in a monograph on the cause of mongolian idiocy (Leipzig, Gevig Thieme, 1939), stated that he found evidence of ovarian insufficiency in 29 of 33 mothers of mongolian idiots. Schröder studied 60 mothers of mongolian idiots from the gynecologic and endocrine standpoints. He also studied the mothers of 60 normal children. In 11 of the 60 mothers of mongolian idiots various disturbances were found which pointed to ovarian insufficiency. Similar evidence of dysendocrinism was found in 18 of the control mothers. Ovarian insufficiency is therefore not more common in mothers of mongolian idiots than in other women. Geyer's hypothesis that the ovarian insufficiency causes an injury to the ovum is untenable.

SAVITSKY, New York.

## Treatment, Neurosurgery

FURTHER OBSERVATIONS ON THE USE OF ADRENAL CORTEX EXTRACT IN THE PSYCHOTIC AND NON-PSYCHOTIC PATIENT. C. A. LOEHNER, Endocrinology **27**:378 (Sept.) 1940.

Loehner reports on the effect of parenteral administration of adrenal cortex extract on a mixed group of 14 patients with psychiatric, medical and surgical conditions. In addition to the daily injections of the adrenal cortex extract, the patients were placed on a low potassium diet and were given 7 Gm. of sodium chloride three times a day.

Two patients with manic-depressive psychosis, manic phase, responded favorably to adrenal cortex therapy, but those with the depressed phase showed little improvement. The response of 4 patients with dementia praecox has been encouraging. Three patients with psychoneuroses of different types responded well to this treatment, as did a similar number of patients suffering from asthma. A patient who

had been subjected to thoracoplasty and had been unable to gain weight or strength after the operation made striking improvement. Another surgical patient, with postoperative paralytic ileus, recovered rapidly after the first injection. The author believes it possible that a patient with retarded or poorly integrated function of the central nervous system is subject to debilitation of the adrenal cortex as a result of the low threshold of the central nervous system to sympathetic stimulation. Since the regulation of potassium metabolism is a function of the adrenal cortex, a depleted cortex leaves the person vulnerable to fluctuating levels of serum potassium, which may reach toxic proportions. PALMER, Philadelphia.

FEMINIZATION AND DEMASCULINIZATION OF A 17-YEAR-OLD GIRL BY INJECTIONS OF STILBESTROL. H. LISSER, Endocrinology **27**:385 (Sept.) 1940.

Injections of stilbestrol (4, 4-dihydroxyalphabetadiethylstibene) were administered to a girl aged 16 years and 8 months who had never menstruated, completely lacked breast development and had an enlarged clitoris and marked masculine hypertrichosis. Normal breast growth resulted within the first month of treatment, although the dose first employed was relatively small. Her first menstrual period occurred five months after beginning of treatment; the stump of the clitoris, previously amputated, atrophied, and the abnormal hair on the body and extremities paled and partially disappeared.

It is noted that the tissue most sensitive to estrogens is the breast, whereas the tissue most sensitive to androgens is the hair follicle. PALMER, Philadelphia.

TREATMENT OF CEREBRAL PALSIES. W. M. PHELPS, J. Bone & Joint Surg. **22**:1004 (Oct.) 1940.

Phelps points out that, according to surveys in various parts of the country begun a few years ago, it may be assumed that there are at least 150,000 cases of cerebral palsy in the United States. A survey of children from 2 to 16 years of age in Maryland showed a yearly occurrence of 7 cerebral palsy births per hundred thousand of population. In other parts of the country surveyed this ratio is fairly constant. The percentage of cases found in the Negro race is much lower than that in the white race. A study to determine what percentage of patients had sufficiently high mental status to become worth while members of society showed that, if the physical difficulties could be alleviated, 68.8 per cent have good mental ability and 72 per cent have a mild or moderate handicap. A large number of patients with cerebral palsy would justify the time and expense of treatment. Severity of involvement is not always a contraindication to treatment. Treatment depends on a careful diagnosis of the particular kind of cerebral palsy: spastic, athetoid or ataxic. A complete muscle examination should be made in all cases. No operation should be performed on a spastic muscle without examination, as the condition of the antagonists is often the deciding factor in determining the procedure. In conservative treatment the flaccid and weak muscles must be protected from the weakening effect of undue stretching and the spastic muscles from the strengthening effect of the stretch reflex. With selective massage, careful exercise, appropriate splinting and protection a great change in muscle balance may be attained. This amount of surgical treatment apparently necessary at first will be greatly diminished. In cases of athetosis a muscle examination will demonstrate those muscles which move involuntarily and those which do not. Athetosis seems better conceived as an involuntary attempt to move a joint in a certain way than as an involuntary stimulation of any individual muscle. Therefore surgical intervention on the muscles, nerves or tendons has little effect. Joint stabilizations are exceedingly difficult. The discomfort of the patient following the operation is marked, and there is much difficulty with pressure sores. In general, operative procedures are unsuccessful. In cases of severe athetosis Putnam's procedure is helpful; it quiets the athetosis but does not increase function. The further use of curare should be watched with interest. Carefully graded

and prolonged relaxation beginning with the least athetoid parts of the body and extended to the more athetoid extremities combined with motion from the relaxed position eventually brings satisfactory results. The treatment of ataxia is that of training the voluntary motor centers to take over the function of the damaged balance mechanism. It can be compared to the learning of any other skill, such as playing the piano, which in time is carried out almost without thought. Thus, with sufficient practice the skill of balance and directional control can be learned until eventually it becomes habitual. The ideal place to train these patients is in a school or institution where their physical and educational needs are met until such time as bad habits can be broken and rehabilitation carried out. There is great danger of old habits returning at home, because they are so closely bound up with the home environment. After discharge from the institution, treatment should be continued individually at least three times a week to insure fixation of progress. It should be decreased gradually over a period of years as skills are taught which take the place of exercises. Obtainable results lie in three fields—use of the legs, use of the arms and speech. Speech disorders are likewise spastic, athetoid or ataxic, and the same principles of treatment apply. Satisfactory results, judged by the standards of other crippling conditions, are obtained when care and treatment are sufficiently intensive.

J. A. M. A.

TREATMENT OF DELIRIUM TREMENS AND ACUTE ALCOHOLIC HALLUCINOSIS. I. J. SILVERMAN, M. Ann. District of Columbia **9**:291 (Sept.) 1940.

Silverman states that since Feb. 8, 1939 the treatment for alcoholic hallucinosis at the Gallinger Municipal Hospital has been intravenous injection of a hypertonic solution of sodium chloride. Injections of 100 cc., and later of 150 cc., of a 5 per cent solution were given twice a day, with sometimes an initial dose of 200 or 250 cc. There were no deaths in 1939 among the patients without complications who were treated for at least two consecutive days. As a minimal standard for the present, it is suggested that when a patient does not live for forty-eight hours the treatment has not been put into proper effect. The mortality rate among patients with complications was definitely decreased. There were only 4 deaths among patients without complications in 1939 (after February 8), and in none of these instances was the treatment given, for one reason or another. There were 16 deaths among the patients with complications. In the first six months of 1940, 1 patient died for whom a complication was not definitely established. This patient was in the hospital less than forty-eight hours and received an insufficient amount of saline solution. During this six months 327 patients were given the sodium chloride treatment. The effect of the hypertonic solution of sodium chloride is striking in that patients soon become quiet and the period of noisy delirium is usually cut down to an hour, or at the most a few hours. It appears that in some instances delirium tremens has been prevented and in others aborted. The patients first become quiet, then coherent and rational, often losing their hallucinations on the first or second day. If pyrexia has ensued, more rigorous treatment must be pursued. When patients are physically fit they are often sent to the hydrotherapy department for hot cabinet treatments and the Scotch douche to complete the treatment. Vitamins are sometimes used. The specific treatment does not exclude other therapeutic measures. The technic of the intravenous medication is simple. If accidental leakage should occur at the site of injection, no harmful results accrue. Local swelling due to the attraction of fluid from surrounding parts and the initial stinging subside as the fluid accumulates. No sloughing of tissue has occurred and venous thrombosis is rare, causing less trouble than is the case with 50 per cent dextrose. Among the 5,000 or 6,000 injections, there were only 2 reactions such as occur after parenteral administration of isotonic solutions of sodium chloride or dextrose. The rate of flow is best controlled by the height of the cylinder rather than by the clamp. With a 20 gage needle, it usually takes from ten or fifteen minutes to inject 150 cc. of the solution. The apparatus should be watched throughout the injection as the needle may

shift, especially if there has been some leakage, with its consequent swelling and distortion of tissues. Alcoholic psychosis is frequently complicated by other conditions, and such patients should not be denied the benefits of treatment with hypertonic solution of sodium chloride together with such therapy as is indicated for the complication. The sodium chloride treatment decreases the incidence of lobar pneumonia, and the chances of patients with complications are improved. Spinal puncture is unnecessary, sometimes harmful and at times dangerous.

J. A. M. A.

ELECTRIC CONVULSION THERAPY IN MENTAL DISORDERS. L. KALINOWSKY and S. EUGENE BARRERA, Psychiatric Quart. **14**:719 (Oct.) 1940.

Kalinowsky and Barrera describe the technic of administration of electric shock treatment and present arguments for its use in preference to that of metrazol convulsive therapy.

Emphasis is placed on the harmlessness of the treatment if properly given, the absence of fear and anxiety both before and after treatment and the possibility that changes in the nervous system may be less irreversible than those produced by metrazol and insulin. The treatment is recommended as an extrahospital procedure because of the absence of sequelae. The possibility of controlling the treatment, from the production of petit mal seizures of varying degrees to full convulsions, and the certainty of obtaining the immediately desired result (the convulsion) would alone recommend it, other factors being equal.

In the 15 cases studied and the 100 cases cited, manic-depressive psychoses appeared to give the best responses. In cases in which treatment was given in the first six months of the psychosis a recovery rate of 80 per cent is cited.

SIMON, Worcester, Mass.

USE OF HISTAMINE IN TREATMENT OF NEUROVASCULAR HEADACHE. W. L. REID, M. J. Australia **2**:307 (Oct. 5) 1940.

Reid gave small repeated subcutaneous doses of histamine to 5 patients with the neurovascular type of headache. One patient experienced only partial relief, while the other 4 obtained complete relief. Each patient, after the possibility of an intracranial pathologic lesion was excluded and the reaction to an intradermal test injection of histamine was found to be positive, was given graduated doses of histamine in the following manner: The solution used consisted of 1 mg. of histamine dissolved in 10 cc. of physiologic solution of sodium chloride. On the first and second days 0.05 mg. of histamine (0.5 cc. of the solution) was injected subcutaneously twice a day, and on the third and fourth days 0.075 mg. (0.75 cc. of the solution). Thereafter, up to the end of the third week, 0.1 mg. (1 cc. of the solution) was given twice a day. When this course was finished, each patient was given one injection of 0.1 mg. of histamine once a week. If the patient remained free from symptoms during the next two or three months, an attempt was made to decrease the dose by spacing the injections. If the symptoms recurred after the dose was diminished, the injections were again increased to one a week. The author applies the term "neurovascular headache" because there is fairly conclusive proof that the aura and pain in many complaints of head pain are due to a disturbance of the neurovascular mechanism controlling certain intracranial and extracranial blood vessels. Of the various patterns of this group, migraine is perhaps the best known. There are several other patterns which have a neurovascular mechanism, and some of these are as common as the classic migraine. It is emphasized that the use of histamine must not be regarded as a cure-all for every type of headache. Each case must be thoroughly investigated, and only when all possibility of a pathologic lesion has been excluded should a neurovascular mechanism be considered.

J. A. M. A.

TREATMENT OF ABSCESS OF THE BRAIN. STUART N. ROWE, Confinia neurol. **3**:96, 1940.

Rowe discusses the various technics that have been used in the treatment of abscess of the brain, but states that no fixed routine should be followed in every case, rather that the method of surgical approach should depend on the manifestations present in the individual case. The interval between the onset of symptoms and the optimum time for drainage depends largely on the patient's condition and in particular on the degree of increase in intracranial pressure. Danger of medullary collapse or rupture of the abscess from too long delay more than balances the danger of meningitis from too early drainage.

Rowe states that the method of treatment which seems to be of value in the greatest number of cases is a two stage drainage, with the insertion of a soft rubber tube. Extirpation without opening of the abscess is advisable if there is reasonable evidence of firm encapsulation. DE JONG, Ann Arbor, Mich.

BELLADONNA IN THERAPY OF ENCEPHALITIS. F. SCHEIFFARTH, Deutsche med. Wchnschr. **66**:318 (March 22) 1940.

Scheiffarth reviews observations made in the course of treatment of encephalitic and other extrapyramidal disturbances. In his discussion of the pharmacologic therapy of extrapyramidal motor disturbances he is concerned chiefly with those forms which belong to the amyostatic symptom complex, that is, to the anomalies of the tonus. The fact that the motility disturbances, hyperkinesias and compulsion movements are hardly at all influenced suggests that the limited success of therapeutic measures is due not so much to etiologic factors as to localization and to physiologic differences. It is known that morphologic changes in the substantia nigra and the striatum are the anatomic foundations of those disturbances in tonus which are found in some of the extrapyramidal diseases, the so-called amyostatic syndrome. However, the localization of the tonus centers does not completely explain the nature of this syndrome. When the reactive organ, the muscle fiber, is considered it becomes evident that among other factors the colloidal condition of the sarcoplasm plays a part in the maintenance of the tonus. The clinical aspects of the amyostatic symptom complex indicate that not only the sympathetic but under certain conditions also the parasympathetic portion of the autonomic nervous system plays a part in tonus regulation. The drugs generally used in the therapy of the disturbances in tonus exert a paralyzing effect on the parasympathetic division. Extracts of belladonna root have been found to have therapeutic advantages over pure alkaloids, and to explain this superiority of the root extracts it has been suggested that they contain associated substances not detectable by chemical analysis. It must also be considered that the alkaloids and the apoalkaloids of belladonna root have a peripheral and a central point of action. The author thinks that the peripheral point of attack is not sufficiently considered in the pharmacotherapy of tonus disturbances. He describes the mode of administration of extract of belladonna root which is employed at his clinic and discusses the selection of cases, pointing out that he uses root extracts only in cases in which the amyostatic syndrome (rigor akinesia) predominates. He found extract of belladonna root particularly effective in post-traumatic akinesia and in the post-traumatic disturbances of the sympathetic regulation. The latter, like sympathetic symptoms that accompany chronic encephalitis, are the manifestation of a lesion of the brain stem. J. A. M. A.

GLOSSOPHARYNGEAL AND TRIGEMINAL NEURALGIA AND ITS TREATMENT WITH SNAKE VENOM. W. BEHRMANN, Deutsche med. Wchnschr. **66**:817 (July 26) 1940.

Behrmann knows of no systematic investigations on the use of snake venom in the treatment of neuralgias in the region of the face and head. He reports 3 cases of his own in which he resorted to this treatment. The first patient, a

woman aged 54, for five months had suffered from severe pains in the tongue. Lightning-like, extreme pains were felt first after eating and later when opening the mouth or speaking. Several weeks later peculiar taste sensations were experienced. The swallowing of dry foods became painful and later impossible. Treatment with various analgesics and with nonspecific vaccine therapy was ineffective. Snake venom, in the amount of 0.25 cc., was injected deep into the muscle. This dose was increased after an interval of three days to 0.5 cc. and later to 1 cc. Injections of 1 cc. of the venom were administered once or twice weekly. After three weeks of treatment the patient was entirely free from pain, and her general appearance was greatly improved. She gained in weight and has remained free from pain for over a year. The second patient had trigeminal neuralgia. Ten injections of snake venom produced complete freedom from pain. In the third patient with trigeminal neuralgia the effect of snake venom therapy was not so favorable. This woman, however, had leontiasis ossea, and the anatomic changes in the cranial bones were responsible for the neuralgia. In the other 2 patients there existed general and cerebral arteriosclerosis. Arteriosclerotic neuritis is especially likely to develop in the trigeminal nerve because its root area has few vessels and is exposed to pontile circulatory disturbances. Snake venom, in addition to the analgesic action, possesses cytolytic and proteolytic effects on the vascular endothelium. It reduces blood pressure, produces a more favorable circulatory state, increases the metabolism of the nerves and counteracts the neuralgic pain.

J. A. M. A.

Vaccine Therapy of Radicular Symptoms in Tabes. L. von Angyal and K. Gyárfás, Monatschr. f. Psychiat. u. Neurol. **102**:65, 1940.

Von Angyal and Gyárfás used Hilgermann's living, avirulent culture of spirochetes in the treatment of 19 patients with tabes dorsalis. Fifteen members of the group complained of lancinating pains and 11 had gastric crises. The vaccine was administered subcutaneously in the thigh at intervals of fourteen days, and from one to twelve injections were given. In most cases painful local reactions, sometimes purulent in nature, were observed. Lancinating pains, paresthesias and crises were commonly provoked by the treatment, and fever, malaise and headache were noted in many instances. Lightning pains were abolished in 5 cases, and their severity was considerably decreased in 6 cases. Gastric crises disappeared completely in 2 cases and became milder in a similar number, with temporary alleviation of the symptoms exhibited in 5 additional cases. One patient showed complete recovery from ataxic disturbances, and 3 displayed lessening of such symptoms. As a rule, the improvement began to manifest itself after the first or second injection of vaccine. It is believed that this form of therapy favorably influences the disturbances usually attributed to radicular irritation, but in evaluating the data no consideration is given to the fact that most of the patients received other types of treatment.

Rothschild, Foxborough, Mass.

## Special Senses

Site of Disturbance in Adie's Syndrome. Harold G. Scheie, Arch. Ophth. **24**:225 (Aug.) 1940.

Adie's syndrome, which consists essentially of tonic pupillary reactions, with or without the absence of the tendon reflexes, has been described under various names: myotonic pupil, pseudo Argyll Robertson pupil, Markus' pupil phenomena and pupillotonia. Adie was one of the first to show a relationship between the tonic pupil and the absence or diminution of the tendon reflexes. He also empha-

sized the necessity of differentiating the condition from tabes dorsalis. The pupillary differentiation is rather interesting. Scheie's table of the differentiations follows.

*Points of Differentiation Between Tonic Pupils and Argyll Robertson Pupils*

| Tonic Pupil | Argyll Robertson Pupil |
|---|---|
| 1. Unilateral, 80 per cent | 1. Bilateral, 95 per cent |
| 2. Convergence reaction: | 2. Convergence reaction: |
| (*a*) Slow gradual contraction | (*a*) Prompt contraction |
| (*b*) Slow gradual dilation | (*b*) Prompt dilation |
| 3. Accommodation reaction: Ciliary muscle may contract and relax slowly | 3. Accommodation reaction: Ciliary muscle not affected |
| 4. Light reaction: | 4. Light reaction: |
| (*a*) Slow contraction | Absent |
| (*b*) Slow dilation | |
| 5. Dilates normally with atropine | 5. Dilates poorly with atropine |
| 6. Normal or semidilated | 6. Miotic |

Scheie postulates that the lesion is a partial sympathetic denervation peripheral to the ciliary ganglion.

SPAETH, Philadelphia.

BITEMPORAL HEMIANOPIA OF TRAUMATIC ORIGIN. JOHN W. HENDERSON and C. WILBUR RUCKER, Arch. Ophth. **24**:800 (Oct.) 1940.

Bitemporal hemianopia is an infrequent result of injury to the head. Østerberg reviewed the 32 such cases reported and found in most of them certain common features. Blunt violence applied to the front of the skull caused a relatively slight fracture that did not extend to the region of the sella turcica but caused a rupture of the skull cap; the patients were comparatively young men of about 30 whose skull bones consequently were rather plastic. Henderson and Rucker report a further case supporting Østerberg's impressions. Østerberg pointed out that there are no anatomic grounds for supposing that the central portion of the chiasm has a separate blood supply. He posed the question why the crossing fibers only should be put out of action by a lesion of the chiasmal vessels. After experiments in which he stretched normal chiasms removed at necropsy, he found that multiple minute tearings occurred in the crossing bundles, whereas the noncrossing bundles were spared. He expressed the belief that in some fractures of the frontal bones the brain may be suddenly and violently displaced enough to cause similar lacerations in the chiasm and consequent bitemporal hemianopia.

SPAETH, Philadelphia.

OPTIC ATROPHY ASSOCIATED WITH PERNICIOUS ANEMIA. J. W. ALDREN TURNER, Brain **63**:225, 1941.

Turner describes 3 cases in which optic atrophy occurred in association with pernicious anemia. In 2 of these cases loss of vision was the initial symptom; in the third weakness preceded diminution of vision by six weeks. In each case there was gradual, progressive visual disturbance. Two of the patients had severe anemia and typical neurologic signs. The third showed slight changes in the blood picture and the early neurologic signs of absence of ankle jerks and loss of vibratory sensation over the malleoli. It is thus shown that optic atrophy may be one of the earliest signs of the disease. The visual disturbance is evidenced by pallor of the disk and loss of visual acuity and is characterized by an oblong central scotoma extending laterally from the fixation point toward the blindspot. Changes in the peripheral fields are slight. The condition may be differentiated from tabes by the retention of pupillary light reaction, even in cases of advanced atrophy, and by the occurrence of the typical central scotoma. Tumor may usually be excluded by roentgenograms of the skull and pituitary fossa. In Leber's disease the scotoma is usually paracentral, but in tobacco

amblyopia the change may be identical with that seen in pernicious anemia; it would seem advisable, therefore, to examine the blood and the gastric secretions for evidence of pernicious anemia in cases in which either of these conditions is suspected.

If patients with pernicious anemia presenting optic atrophy are treated early and thoroughly with injections of liver extract, the prognosis for return of useful vision is good, although improvement is slow and some impairment usually remains.

MASLAND, Philadelphia.

## Basal Ganglia

HEPATOLENTICULAR DEGENERATION IN A CASE WITH DISTURBED PROTEIN METABOLISM AND PROBABLE LEAD INTOXICATION. KARL O. VON HAGEN and E. M. BUTT, Bull. Los Angeles Neurol. Soc. **5**:107 (June) 1940.

Von Hagen and Butt report the case of a typesetter aged 25 who died after an illness of about nine months' duration, characterized by increasing drowsiness and apathy, tremors of the extremities, edema, generalized motor weakness and rigidity, masking of the face and slow monotonous speech. The nonprotein nitrogen content of the blood was 34 mg. per hundred cubic centimeters. Eventually the serum albumin was 1.8 Gm. and the serum globulin 2.2 Gm. per hundred cubic centimeters. The lead content of the blood was only 0.05 mg. per hundred cubic centimeters. The spinal fluid was bloody and xanthochromic. Death followed hematemesis. At autopsy there were softening and gliosis in the putamen on both sides, with slight involvement of the adjacent white matter. The brain and meninges were congested. The liver was of normal size, but exhibited periportal fibrosis and proliferation of the bile ducts. The spleen was also diffusely fibrotic, and there was considerable excess fluid in the pleural and peritoneal spaces. Lead was found in excess in the liver and kidneys, but not in the brain. The authors regard the case as interesting because of the association of hepatolenticular degeneration with disturbance of protein metabolism and chronic lead poisoning, although the lead content of the blood was normal.

MACKAY, Chicago.

EXTRAPYRAMIDAL FUNCTION. FRED A. METTLER, J. Nerv. & Ment. Dis. **92**:141 (Aug.) 1940.

Mettler considers extrapyramidal function in the light of recent experimental work. Section of the decussation of the pyramids produces motor weakness without spasticity, and subsequent stimulation of the motor, premotor and prefrontal cortex can still inhibit clonic or tonic states in the limbs, while cortical ablation produces motor rigidity. Possible pathways for these effects are in the extrapyramidal system. The caudate nucleus receives fibers from the cortex and exerts an inhibitory effect on motor activity, since stimulation of this nucleus inhibits movements which have been cortically induced. The globus pallidus is, however, an energizing, and not an inhibiting, structure, since its stimulation increases tonus. The pallidum discharges through three chief circuits, including fibers to the red nucleus, the substantia nigra and the subthalamic nuclei. The red nucleus exerts an inhibitory and the substantia nigra an energizing effect on motor function. The cerebellum, acting through the brachium conjunctivum, thalamus and corpus striatum, influences motor function positively through the substantia nigra. The subthalamic nuclei are also energizing structures and when stimulated produce violent positive motor effects on the opposite side of the body, probably through the reticular nuclei and the reticulospinal tracts. These extrapyramidal circuits obey the law of reciprocal innervation.

Clinical phenomena may be explained by the cautious application of these concepts. Certain tremors may be due to the failure, or dropping out, of elements of the motor system, leaving "scotomas" in the motor pattern. The hypertonus which so often accompanies tremor may be a compensation superimposed on the

original defects. The tremor of Wilson's disease may be explained by the pallidal lesion which disturbs reciprocal innervation, while the rigidity results from secondary interference with the efferent pathways from the inhibitory corpus striatum. In paralysis agitans, on the other hand, the efferent pathways from the striatum are unaffected, so that the tremor is less marked during volitional activity. In Huntington's chorea the inhibitory striatum is chiefly damaged, so that the energizing pallidum is released and gives rise to synergic, reciprocally innervated movements which are cut off from voluntary control. Dystonic and athetoid movements are considered as due to irritative stimuli arising from area 6 of the cortex and passing to the substantia nigra, the inferior olive, the nucleus ansae peduncularis or the globus pallidus. The phenomenon of "waxy tonus" would seem to be due to an irritative lesion of the pallidum with superimposed cortical activity. The spasticity of hemiplegia would likewise be ascribed to damage to the striatum, as well as to the pyramidal pathways.

MACKAY, Chicago.

ISOLATED HEMOCHROMATOSIS OF THE SKIN IN WILSON'S DISEASE. S. THADDEA and H. J. OETTEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:551 (Nov.) 1940.

A youth aged 18 was admitted to the hospital two years after a febrile episode with headache and insomnia, following which he showed an unusual capacity to retain what he saw. His upper lip soon began to twitch, his speech became defective and his writing small. Tremor of the hand appeared, and his tongue became stiff. In the fall of 1937 brown and dirty gray discolorations of his skin appeared, especially of the feet and face. The pigmentation in his face disappeared and became more intense in his lower limbs. Clumsiness and awkwardness became increasingly severe. Masked facies and marked sialorrhea also appeared.

On admission he showed amimia, no spontaneity of movement, dysarthria, defective associated movements in the upper limbs, twitching of the upper lip, rigidity of the lower limbs and intention tremor. He was mentally clear; there was no Kayser-Fleischer ring; the liver and spleen were both enlarged and somewhat tender. The urine showed urobilin; the iron content of serum was 80 micrograms (normal 130 to 150 micrograms) per hundred cubic centimeters; oesophageal varices were demonstrated roentgenographically, and the galactose tolerance curve was abnormal.

The trunk and limbs showed a mild brownish discoloration. Intense pigmentation was noted only on the dorsum of both feet and in the region of the malleoli. In the region of the external malleoli pigmentation was earthen to chocolate brown with black areas. The pigmentation in places was in the form of small macules and in other places in that of a network. The pigment was confluent in the most intensely affected parts. Biopsy of the skin in these pigmented areas showed melanin and iron-laden pigment in the basal layers of the epidermis.

The patient died two days after a splenectomy, on Nov. 6, 1939. Autopsy showed a typical hobnail liver, esophageal varices and blood in the stomach; the brain showed atrophy of the lenticular nuclei; the cells were fewer than normal but showed no degenerative changes. There was no increase in glia cells. No mention is made of the presence of Alzheimer glia cells. Some calcium and iron were found in walls of vessels in the region of the lenticular nuclei.

SAVITSKY, New York.

# Society Transactions

## PHILADELPHIA PSYCHIATRIC SOCIETY

LAUREN H. SMITH, M.D., *President, in the Chair*

*Regular Meeting, Nov. 8, 1940*

### SYMPOSIUM ON PSYCHOSOMATIC RELATIONSHIPS

**Eczematous Dermatitis as a Psychosomatic Phenomenon: Report of a Case.** DR. J. W. MCCONNELL.

A woman aged 60, without profession, in February 1940 suffered a psychic trauma followed by mild depression and agitation. Two days later a profuse, confluent, erythematous eruption appeared, principally over the face and neck; this was followed by insomnia, anorexia, loss of weight and emotional imbalance. There was steady increase of the eruption, which spread to the arms and trunk.

The general habits were good. She smoked occasionally, used wine infrequently, but took no other alcoholic beverages. She did not use cosmetics. The blood count was normal except for a slight increase in the eosinophils. There was no hyperglycemia. Urinalysis gave negative results. The basal metabolic rate was + 2 per cent. The results of general medical studies were without significance.

Rest and local application of a solution of boric acid relieved the itching, and at the end of two months the patient was much better. No allergic studies were made. She was free of symptoms, both mental and physical, in July 1940. A second mental trauma was received in August 1940, with immediate return (in twenty-four hours) of the cutaneous eruption, depression and agitation. This eruption continued, with mild mental depression and emotional instability, for nearly one month. During this time she avoided social activities. Treatment with local soothing applications, general sedatives and tonics cleared all cutaneous and psychic features.

The original tentative diagnosis, which was later confirmed, was that of "generalized eczematous dermatitis associated with a psychopathy." From September 1940 to Oct. 23, 1940, the patient was well. Early in the morning of October 24 her home was partially destroyed by fire. On October 26 she was again depressed and emotional and the face and neck were again the sites of cutaneous outbreak, similar in every respect to the one of February 1940.

#### DISCUSSION

DR. JOSEPH KLAUDER: In commenting on this case, one may ask: "How valid is the diagnosis of a psychosomatic phenomenon in relation to the patient's erythematous dermatitis?" Properly speaking, one cannot label a cutaneous disease psychogenic, since there are no features indicative of psychogenesis. Almost all clinical diagnoses are presumptive in the absence of an irrefutable laboratory test or pathologic examination. Clinical diagnosis is made on what is reasonable from the evidence that is premised. In the case in question this principle of inductive reasoning seems to be fulfilled—"The same cause under the same circumstance produces the same effect." The same cause under the same circumstance on three different occasions produced the same effect. Moreover, the effect was a reasonable one, since the vegetative nervous system is intimately concerned in vascular dilatation, one of the initial processes in inflammation. Vascular dilatation—blushing—is a well known phenomenon after psychic disturbances. The face is the most common location. In the case now under discussion, the erythema appeared principally over the face and neck and later spread to the arms and

trunk. The appearance of the erythema was sudden. It went beyond the vasodilatation incident to an emotional reaction, since there was exudation of serum that characterizes inflammation. For this reason some may object to regarding it as a psychosomatic phenomenon. It is to be recalled, however, that when hypnosis was much in vogue all varieties of cutaneous lesions—erythema, vesicles, bullae, papules, lesions resembling burns, ecchymosis, bloody exudate from a previous dermatographic lesion—were reported as produced through suggestion during hypnosis.

I am asked to comment on the method of studying this patient in relation to the diagnosis of a psychosomatic cutaneous reaction. I note that the results of food tests were negative. These were performed with the purpose of showing that the cutaneous reaction was not allergic. A much more likely explanation of an acute eczema of this nature is not an allergic reaction to ingested food, but an allergic reaction to many of the allergenic substances that cause dermatitis on contact with the skin. This study is carried out by means of patch tests. There is no laboratory diagnosis of eczema, nor can its cause be shown through the demonstration of any clinical or pathologic abnormality. There is only one exception in which an irrefutable cause of eczema or dermatitis can be shown, and that concerns contact with an allergenic substance as shown by the patch test.

I understand it is proper to discuss the general psychosomatic relation to cutaneous disease. In addition to what may be called experimental evidence—cutaneous lesions produced by suggestion in hypnosis—should be mentioned the stigmas of the crucifixion. Elsewhere (Stigmatization, ARCH. DERMAT. & SYPH. **37**:650-659, 1938) I discussed the psychogenesis of stigmas and reported on personal observation of such lesions in the case of Thérèse Neumann, of Konnersreuth, Germany. I do not believe the lesions were self produced. They consisted of a flat, dry, dark clot of blood. The skin around the clot was normal in color and appearance, wrinkled and firmly adherent to the clot. There was no evidence of inflammation, ulceration or destruction of tissue.

I published elsewhere (Psychogenic Aspects of Skin Diseases, *J. Nerv. & Ment. Dis.* **84**:249-273, 1936) a list of diseases of the skin in which psychologic phenomena play a motivating role or a notable determining factor. At the top of the list were cutaneous lesions resulting from vasodilatation, such as erythema, dermatographia and urticaria, acute or chronic, localized or generalized. I listed as other common psychosomatic cutaneous expressions pruritus, localized or generalized; what is commonly called neurotic excoriation; hyperhidrosis; fixed pain, and sensory disturbances (topalgias of Blocq), of which perhaps "burning tongue" is the most common expression. Itching pain may appear at the site of psychic fixation, or it may be the expression of a fatigue or anxiety neurosis, of a mental conflict symbolic of soul pain or of a dermatophobia. The location of itching frequently manifests the influence of events, recollections or conceptions, as was evidenced in these patients. A woman experienced itching each Tuesday and Wednesday night. The itching was regarded as psychogenic in relation to the death of her husband, who died on a Wednesday night and was in a dying state for about twenty-four hours. Another patient had itching of the genitalia, which appeared soon after illicit intercourse during the absence of his wife. In addition, he frequently washed his penis and scrotum, a probable displacement comparable to the washing of the hands of Lady Macbeth.

Neurotic excoriation is essentially a traumatic dermatitis, self produced (not for deception) through an uncontrollable desire to pick, dig or otherwise manipulate the skin. Such manipulation is performed at times after mental stress and strain, and after an emotional upset. This was exemplified by the patient who said: "When anything goes wrong in my work I come home and take it out on my skin." Neurotic excoriation may be seen as an expression of a phobia—usually the fear of parasites. The concept of the patient is that the skin is infected with insects or parasites. The skin is manipulated in order to remove them. This type of patient visits the office with a long list of questions in one hand and in the other a paper containing the corpus delicti—the alleged parasite, but in reality scales.

Some psychoanalysts have suggested that neurotic excoriation is a form of masturbation. Menninger regards the morbid state as an attenuated form of suicide.

DR. MILTON K. MEYERS: I should like to ask Dr. Klauder if psoriasis in his estimation is a psychosomatic manifestation.

DR. JOSEPH KLAUDER: I do not believe so. Jelliffe covered this subject thoroughly.

**Bronchial Asthma: Report of a Case.** DR. LOUIS H. TWYEFFORT.

A 14 year old Jewish girl, to whom I shall refer as Rita, was admitted in December 1938 to the University Hospital for observation. Her chief complaint was that of "palpitation and asthma." Always somewhat nervous, Rita had experienced occasional palpitations during the preceding two years (on exertion, while at rest or in connection with "emotional upsets"). In addition, the patient, subject to asthma when younger, had again suffered from frequent attacks for over a year. The seizures occurred almost daily; there might be three or four in one day. Attacks were also frequent at night. At times she would "gasp for three or four hours." Therapeutic measures had effected some symptomatic relief, but had not reduced the frequency of the attacks. Six weeks previously she had spent three weeks in bed with a "severe cold," at which time the family physician had discovered tachycardia, which was still present on admission to the hospital.

Other symptoms of which she complained were irregular menses, frequent colds, postnasal discharge, increased sweating, intolerance to heat, tremor of the hands, anorexia, loss of 10 pounds (4.5 Kg.) and frequent nausea after meals. Later her appetite had become excessive. In October her basal metabolic rate had been + 35 per cent.

Her childhood asthma had started around the age of 5, shortly after a tonsillectomy and severe attack of cough. She had suffered intermittently from it until she received bronchoscopic treatment at the age of 9, after which she was apparently free of symptoms until its recurrence at the age of 12. (The menses had appeared the previous year.) Subsequently she had been treated with autogenous vaccines, maxillary punctures, suction and epinephrine sprays and by dietary measures. Since childhood she had consulted "at least a dozen physicians" about her asthma.

Both her parents are living, she being the only child. The father has questionable hypertension; the mother, who is nervous and "high strung," claims to have "gallbladder trouble" and had a "nervous breakdown" when the patient was 2 years old.

On admission, the blood pressure was 148 systolic and 70 diastolic; the pulse rate occasionally reached 130 to 140, and there was marked restlessness. The thyroid was not enlarged, and there were no ocular signs indicative of thyrotoxicosis. Moderate tremor of the hands was noted. Laboratory studies revealed a normal sugar content of the blood during fasting and 161 mg. of cholesterol per hundred cubic centimeters; the basal metabolic rate, determined on two occasions, was + 17 and + 9 per cent.

Previous allergic studies, made in the summer of 1938, showed marked reaction to a stock diet, and numerous "moderate" and many "slight" reactions to other allergens.

Also, at this time the patient's intelligence quotient (by the Otis test) was 113; her mental age was 16 years 11 months and her chronologic age 14 years 10 months.

The general clinical impression was that the patient was suffering from bronchial asthma, as well as from mild hyperthyroidism, the latter possibly being aggravated and complicated by the asthma and by the habitual use of epinephrine.

During her twelve days of hospitalization, during which she did not receive specific therapy, Rita had no asthmatic seizures and recovered from mild bronchitis. Just prior to her discharge a series of roentgen radiation treatments of the neck and chest was instituted.

Her referring physicians had already suspected that emotional factors connected with her home environment might be playing a contributory role in her asthma. A psychiatric consultation was requested, after which she spent seven weeks in a convalescent home, returned to her family and from then was followed regularly by the allergist, the internist and the psychiatrist.

She was seen in four psychiatric interviews during the first month and on six occasions in the subsequent year and a half. From the time she returned to her home, she reported marked improvement in both the incidence and the intensity of her asthma, although she was not receiving any special medication except a mild sedative, to be used in emergencies. For a while she continued to have three or four mild seizures a month, as against her previous almost daily ordeals. During the past six months she has had but one severe attack. Furthermore, both she and her mother claim that during August her hay fever was much milder than in previous years and that during the past winter she did not suffer from colds, whereas formerly they had been of constant occurrence.

From the first of the psychiatric interviews, it became apparent that three sets of emotional factors were playing an important role in the tension to which Rita was constantly exposed in her home environment: first, an unfortunate adjustment of the parents to each other; second, a difficult mother-child relationship, and, third, the child's own personality.

Almost the first words of the patient when coming under treatment were: "I feel I need a complete rest from all of my family . . . I am sure that I will start feeling badly again when I get back to my mother's." I shall let Rita herself describe her parents: "Father—quiet, easy-going, level-headed, cool. Mother—very nervous, high strung, quickly resentful. She has always wanted me to hang on her apron strings . . . If I were fifteen minutes late from school, I'd be on trial for my life." The mother's extreme neuroticism was evident. During interviews her protestations of devotion to the child were repeatedly punctuated by outbursts of weeping. The mother had not wished for more children "because Rita's health had been so poor."

The child told of bitter quarrels between the parents. "Mother yells; father never raises his voice." On these occasions the mother had frequently threatened to leave the father. When the patient explained, "I know how that would hurt him," she wept copiously. "Father is ready to settle down. Mother is 12 years younger and wants to do things."

As to the patient herself, she was a hyperkinetic, intelligent girl, precocious verbally, intellectually and in her appearance and general attitude, although emotionally still a child. Her chief interests centered around reading and her studies. She declared that she had no interest in boys. (Romantic novels were "a waste of eyesight.") She referred to herself as a determined person.

The interactions of this family of three, their attitudes toward each other, toward the patient and toward her asthma are summarized in Rita's own declarations: "Father gives me most everything I ask. When I have my attacks of asthma, he waits on me . . . My asthma hurts mother more than it does me . . . In her attentions to me mother is thicker than molasses. She has always wanted me to hang on her apron strings. I resented it and still do. She is so solicitous, so dictatorial. It is always: 'Don't this; don't that.'" The mother, seen separately, gave confirmatory evidence of these assertions.

During interviews, the patient made a number of interesting spontaneous observations about her asthma. She mentioned that her attacks occurred whenever she became excited or faced some trying situation. She herself had noticed how an attack would appear invariably within a half-hour after her parents had quarreled. "These quarrels used to be terrible messes . . . My parents' arguments would make me boil inside and make me feel like running away . . . When the attacks occur in my sleep, they may be due to a subconscious rehearsing of the events of the day . . . Exercise probably does not bring them on, but getting upset and arguments will."

Later in treatment Rita again remarked spontaneously: "One can control the attacks a great deal. Much of the coughing acts as a means of getting sympathy."

The actual therapeutic procedures employed with Rita were of the simplest. She was allowed to tell her story freely, without criticism. In objective fashion she would view her own reactions to the particular situation, as well as her mother's reactions and the underlying reasons for her mother's attitudes.

Confirmation of Rita's changes in attitude appeared in the mother's statements after a few months. "Rita is much less tense at home . . . much more agreeable . . . She's much easier to reason with now . . . Her reactions are much more grown up . . She's entirely different in her makeup."

A number of Rita's spontaneous productions, already referred to, suggested a fair degree of insight from the start. Her insight became more valuable to her when through the treatment relation she was encouraged to feel what she had suspected as true, that it actually possessed validity. She made a rather pertinent observation when three weeks ago she declared: "I recently told mother that all this would not have happened if I had not been an only child."

**Hyperthyroidism, with Somatic Difficulties on a Psychologic Basis: Report of a Case.** DR. BALDWIN L. KEYES.

A white woman aged 26, married, a housewife, with 1 child, was admitted to the hospital on Sept. 2, 1940.

The chief complaints were enlargement of the neck for one year; nervousness, irritability and excitability for one year; excessive perspiration for six months; frontal headache for "several" years; shortness of breath on exertion and easy fatigue for six months; swelling of the ankles and hands for four months; protruding eyes for five months; loss in weight, of 14 pounds (6.4 Kg.), over a three month period; insomnia for one year, and scanty menses for eight months.

*Family History.*—The father died at the age of 30, of pneumonia; the mother, now 47, has phlebitis and hypertension. The sister died at the age of 21, of tuberculosis. The patient has 1 daughter, aged 5. One child died at the age of 3 months. There was no history of mental, malignant or chronic infectious disease other than those already mentioned.

*Past History.*—The patient had had chickenpox, diphtheria, pertussis and measles in childhood, without sequelae. She suffered from dysmenorrhea. Appendectomy had been performed at the age of 24 and tonsillectomy at 11.

*Personality.*—The patient was outgoing and restless; she liked being with people and was rarely alone. She was ambitious and always had an abundance of energy and enthusiasm.

*Physical Examination.*—The general physical condition was normal except for urinary frequency, burning and nocturia since the age of 10, when she had an infection of the urinary tract.

On examination the patient was excitable and restless; there were coarse tremors of the extremities, and the skin was warm and moist.

Examination of the eyes revealed exophthalmos, lagging of the lids and difficulty in convergence.

Tremor of the tongue was present. The upper teeth were false, and the tonsils had been removed.

There was diffuse, soft enlargement of the neck, and a systolic bruit was heard over the cervical region. The heart was enlarged 2 cm. to the left of the midclavicular line; the apex beat was heard in the sixth interspace, where a muffled systolic bruit was evident.

*Laboratory and Clinical Data.*—The basal metabolic rate was +8 per cent Tachycardia was noted. Substernal thyroid was not evident. The cholesterol content of the blood was 140 mg. per hundred cubic centimeters. The blood count (including the differential) was normal. The Wassermann and Kahn reactions of the blood were negative. Results of hepatic function tests were normal.

*Course in Hospital.*—The patient was treated with solution of potassium iodide, rest in bed and phenobarbital. On September 9 (one week after admission) the basal metabolic rate was + 45 per cent and the pulse rate 90; on September 14 the basal metabolic rate was + 23 per cent and the pulse rate 74. The patient was transferred to the surgical service on September 17, and subtotal thyroidectomy was performed on September 18. She reacted well to the operation and had an uneventful convalescence. She was discharged to her home on October 2.

*Psychiatric Interviews.*—The patient was first seen on September 11. It was explained to her that I saw patients with conditions like hers routinely and that emotional disturbances might in some way be related to the illness. The following day, while the psychiatrist was passing the ward, the patient beckoned to him, said that she had not slept the night before, when she recalled a great deal she had never told any one, and asked if she might tell him. The following events, in chronologic order were, the patient said, of great emotional importance to her.

Her father died when she was 6, a year after her sister was born. The mother managed a restaurant and cared for the children as best she could, tending to be openly apprehensive about their welfare; she was rather solicitous about them. Both children depended on the mother for affection and guidance.

When the patient was 25, her sister, whom she described as "my only pal, to whom coming to live with the family began making sexual advances to the patient. The patient was extremely anxious both to hold him at a distance and to keep her mother ignorant of the stepfather's attempts. Although repeatedly rebuffed, his advances never ceased, and the patient married after graduation from high school, at the age of 18, largely to get away from the stepfather. Even after her marriage she found little rest from him. He would come to her home while the patient's husband was away. This situation persisted until the patient was 23, when, with guests in her home and her husband away, the stepfather arrived, warning her he planned to outstay all guests. The hour grew late; he went upstairs, and, when the guests had gone, she found him dead on the floor of the bathroom. The diagnosis was heart failure. The patient did not sleep well for many months and finally confided in her sister, who returned the information that he had made similar advances to her. Presumably, the mother never knew.

At the age of 20 the patient had her first child, who died when 3 months old. At 21 she gave birth to her second child. The husband, an emotionally immature and irresponsible man, could not seem to hold a position. The patient was ambitious for social and material gain. Marital relations became progressively less satisfactory. The husband returned to his home more and more often, and the patient became dependent on her mother for moral and financial support.

When the patient was 25, her sister, whom she described as "my only pal, to whom I could tell everything," was taken seriously ill with pulmonary tuberculosis. The patient became "nervous" and irritable and lost weight. The sister was taken to a sanatorium, where she died four months later, after a thoracoplastic operation. The patient's symptoms of hyperthyroidism, already begun, increased progressively until hospitalization.

In the past year the patient's husband had shown no sympathy for her distress, had expressed resentment at her rebuffs of his advances and had begun to keep company with other women; at the time of her hospitalization they were preparing to separate.

The patient was seen for the third time on the following day, September 13. She was sleeping during the midmorning (which she had been unable to do before) and stated she had slept all through the previous night, for the first time since her admission. Coincidentally, at least, a basal metabolic test on the following day showed a decline in rate from + 45 to + 23 per cent (the patient was still receiving medication).

On discharge from the hospital, on October 2, the patient asked to return to the hospital's outpatient department for further psychiatric help. She was next

seen on October 29, when she complained of insomnia, fatigue during the day, an occasional feeling of choking in her throat, a sensation of hardness about her chest and considerable emotional lability. Since leaving the hospital she has taken her child and returned to her mother's, is definitely separated from her husband, is planning to work, thereby earning money for a divorce, and is fearful lest the husband steal the child or do violence to the patient.

DISCUSSION ON PAPERS BY DR. TWYEFFORT AND DR. KEYES

DR. LOUIS TUFT: I have been much interested in Dr. Twyeffort's presentation, not only because I studied this patient from the allergic standpoint, but also because of the striking benefit derived from psychotherapy. In a condition like allergy, many attempts have been made to explain the mechanism, these explanations being based on biochemical factors, endocrine influences and, more recently, psychic upsets. I have never been particularly impressed with the idea that psychic or emotional upsets could primarily produce the initial attacks of asthma. One reason for this viewpoint is my experience that certain allergic conditions could be induced repeatedly by material allergens. For example, in a patient with hay fever whose symptoms were limited definitely to the pollen season, we could induce the symptoms at any time by nasal instillation of ragweed pollen. Certainly, there could not be anything psychic about that. It is true that one patient may suffer more with his hay fever than another, but that has nothing to do with the essential cause of hay fever. There are many other instances in which definite manifestations can be induced by specific sensitivity. For example, one may induce an attack of asthma by having the patient inhale dust. I have never been impressed, however, with the idea that an attack of asthma could be initiated in a person who was not otherwise so predisposed. I feel that psychic manifestations can act as secondary or aggravating influences in a person who is basically asthmatic. I should place psychic trauma in the same classification. Dr. Twyeffort's case is a fine illustration. Here is a girl who had a definite allergic background, a strong positive family history of allergy, a girl who had asthma in childhood and who had allergic rhinitis. There is no question of an allergic basis. However, her asthma was not responding to treatment, and all the methods of therapy we ordinarily use failed to relieve the asthma. It was only when the thyroid condition supervened that the emotional factor came to the fore and was well controlled by the method Dr. Twyeffort described. Now it is true that the girl was rid of her asthma during that period, but I first saw her in the fall. She went to the hospital in January, and she was free from symptoms until I saw her again, late in July. It was then recalled that she had had symptoms of hay fever the year previously and had given a positive reaction to ragweed. Pollen therapy, therefore, was begun in July, so that the patient received therapy only adequate to give her slight relief but not sufficient to overcome all her symptoms. She was relieved of the hay fever to some extent, but not of the asthma. The following year, when she was under treatment, she had mild symptoms of hay fever and mild asthma during the pollen season.

In this case, therefore, the patient was definitely sensitive to certain specific allergens and asthma was provoked by an emotional factor. If the emotional factor had been overlooked the patient might have continued to have asthma. It is important, however, that one should not attempt to explain all asthma on a psychic or an emotional basis. On the other hand, the allergist, likewise, must not lose sight of the fact that it is necessary sometimes to search for a possible psychic factor in asthmatic patients who do not respond to the usual methods of treatment.

DR. EDWARD ROSE: After hearing the report of Dr. Twyeffort's case, one may be entitled to wonder whether Rita was suffering from a hyperplastic toxic thyroid or from her neurotic mother. The answer is, perhaps, "Fifty-fifty."

The ultimate cause of the pathologic mechanism which produces hyperthyroidism, of course, still eludes one, in spite of the various attractive theories,

none of which has been proved. Nevertheless, the importance of psychic and emotional factors in acting not only as a trigger mechanism but also as an aggravating influence in a preexisting thyrotoxic condition has long been recognized.

A number of years ago, Dr. Warthin propounded a theory by which he attempted to prove that exophthalmic goiter occurred only in patients with a certain constitutional habitus—Graves's constitution. Much was written about the matter and there was much talk, but the burden of his contention was that if one looked closely enough into the background of thyrotoxic patients, especially if one saw them in their prethyrotoxic phase, one could detect certain traits, physical and emotional, such as slight prominence of the eye, tendency to sweat and easy emotional excitement. There is something in this. Although I do not believe the idea was entirely true, the importance of these factors is undeniable. I believe that we internists and surgeons do not use psychotherapy as much as we should in the management of thyrotoxicosis. It is a useful weapon. However, in treating a patient with full blown thyrotoxicosis we must remember that the usefulness of psychotherapy is limited by the fact that a considerable period is involved. There would be considerable chance that some organic complication of hyperthyroidism, such as a cardiac or hepatic crisis, would develop. The usefulness of psychotherapy, I believe, is limited. Nevertheless, it is and can be made even more useful if we utilize it in attempting to help the patient adjust after a successful operation or after roentgen treatment.

There remains another group of patients who present a borderline picture of thyrotoxicosis which it is frequently difficult to diagnose. The appearance may be highly suggestive of hyperthyroidism, and yet certain important factors may be lacking to the completion of a satisfactory diagnostic picture—tachycardia, slight fulness of the thyroid, fine tremor, tendency to sweat, increased basal metabolic rate (frequently the basal rate is on the borderline of or in the upper range of normal), slight loss of weight or inability to gain or an irritable gastrointestinal tract. I have seen cases in which, even after two or three years of observation, the physician hesitates to operate.

We have been handicapped by lack of objective methods of diagnosis. Within recent years two advances promise the possibility of our acquiring some such methods. One is the development of the technic for the determination of iodine in the blood. Another weapon, which gives much more promise, is the galactose tolerance test. Althausen, Lockhart and Soley, of the University of California (*Am. J. M. Sc.* **199**:352 [March] 1940) have published their results with this test. Abnormal galactose tolerance was found in cases of hyperthyroidism, hepatic insufficiency and Paget's disease of the bones.

I had the opportunity to study the patient presented by Dr. Twyeffort. I saw her this morning and found she has had no asthmatic attacks for a long time. There is no evidence of thyrotoxicosis at present.

**Gastrointestinal Symptoms: Report of a Case.** DR. O. SPURGEON ENGLISH.

The patient is a second year high school girl aged 15, living in the suburbs of Philadelphia. Her chief complaints are attacks of vomiting for the past year. Between the attacks she has a poor appetite, with belching of gas and constipation. At times, instead of vomiting, there is gastric distress with distention and marked belching of gas for a period lasting from one-half to one hour, followed by relief.

*Family History and Background.*—The father of the patient died when she was 3 years of age. He was described as a nervous, irritable, seclusive man, whose death was due to pneumonia. The mother is living and working as a secretary. She is a small, very intense person, who for the past eight years has suffered from migraine headaches occurring from once a week to once a month. Since the death of the father the mother has had to work outside the home most of the time to support a family of 3 children.

The patient was a premature baby of 8 months. She was described as a sensitive, frail, frightened infant and child. She suffered from poor digestion from birth. She was nursed for four months and then weaned. There was continued "indigestion" until she was 1½ years of age; then a suitable formula seems to have been found, and from that point she grew well. She was always a light sleeper, and it was difficult to get her to rest in the afternoon. There was no difficulty in toilet training, and she adapted well to school until possibly the past year or two.

Inquiry about the patient's emotional development revealed that she was "horribly upset" when she heard about menstruation from her mother, at the age of 12. Discussion left her hysterical for several days, and her mother feels that ever since menstruation began the patient has not been as well as before. Her periods have been irregular and accompanied by some pain, dizziness and nausea. Recently sleeplessness has increased around the time of the menstrual period.

Inquiry into the school situation revealed that at the end of 1939 she joined a girl's club, consisting in all of twelve girls. For some reason, the leader of the group took a dislike to her and seemed to be able to turn the rest of the group against her. She finally was forced to withdraw from the club. During 1939 and 1940 anorexia grew worse, with either belching or vomiting following the ingestion of food fairly frequently. Once in the spring of 1940 she lost her voice for three weeks and was able to speak only in a whisper.

Examination of the patient reveals a very attractive girl, with a friendly, though somewhat reserved, manner. No laboratory or roentgen examinations of the gastrointestinal tract have been made. This record, without an extensive roentgenographic study of the gastrointestinal tract, is purposely presented. Physicians have to meet the problem of treating many such patients who cannot afford roentgenographic study. Can psychiatric treatment justifiably be started without expensive roentgenographic study, and, if so, what are the problems to be encountered?

DISCUSSION

DR. GUY M. NELSON: I shall first discuss "expensive roentgenographic study." Times have changed in this country. No matter what one wants to believe, the old days of large unearned incomes, of large salaries are past, and the days of expensive roentgen studies should be past. We, in the medical profession, should see that they are past, before the government is given the excuse to intervene.

Next, should the patient be sent to a psychiatrist on the basis of the records presented by Dr. English? I think she should, and without further studies, for the history shows that the father was nervous, irritable and unstable and the child has become unstable at the periods in her life in which emotional upsets have occurred.

What are the problems to be encountered in persuading the patient to have psychiatric treatment? The greatest difficulty in this case will be to persuade the patient and the patient's mother that psychiatric aid is indicated. It is patients of this type who, after ten or fifteen years of treatments and operations, have such habit pathways established in the brain that it is impossible to eradicate them. I often ask the patient whether he thinks he could learn without instruction to use a typewriter or whether it would be easier to go to school for the purpose. Most say that going to school is the proper way. Then I transfer this to the problem in hand. "You need to go to school. Psychiatry is a matter of education, and you need a tutor to explain the emotions, the conscious and the subconscious mind to you. You need to learn how to handle them."

In certain cases roentgenographic study may be required to convince the patient that the psychiatrist is careful and attentive, and that he knows the patient's problems. An internist may make the mistake of regarding an actual organic condition as psychiatric, and the opposite may also be true.

**Cardiovascular Disturbances: An Evaluation from a Psychosomatic Standpoint.** DR. JOSEPH C. YASKIN.

Neurotic symptoms are frequently found in association with organic cardiovascular disease. These represent the reactions of the neurotic traits of the patient's personality to the organic situation and require a careful clinical evaluation for therapeutic purposes.

The more common cardiovascular symptoms unaccounted for by any primary organic lesion include precordial consciousness and pain, disturbances of cardiac rate and rhythm, fears of cardiac death, disturbances in blood pressure, abnormal blushing of the face, ears and upper part of the thorax, abnormal perspiration of the palms and congestive disturbances of the nose and extremities.

For therapeutic purposes, the exclusion of primary organic disease is, by itself, an unsatisfactory criterion for establishing a diagnosis of neurosis or psychoneurosis. For successful treatment it is imperative also to establish an etiologic diagnosis. The various cardiovascular symptoms are only a conspicuous part of the total neurosis. Anxiety is the central symptom of all neuroses and psychoneuroses. The etiology, psychopathology, prognosis and treatment vary with the several types of neuroses and psychoneuroses.

Two cases are reported. In both the patients were men and in both the condition was of many years' duration. In one the symptoms were predominantly cardiac, with attacks of panic, and in the other, pathologic blushing, obstructive congestion of the nose and feelings of inferiority were present. By the free association method, an actual incest relation with a sister was traced in each case, and considerable improvement followed the treatment.

DISCUSSION

DR. FRANCIS CLARK WOOD: I should like to say a few words about the clinical differentiation of cardiac neurosis and organic heart disease. Patients with either of these conditions may suffer from shortness of breath, palpitation and pain in the chest. In the majority of instances the recognition of the true nature of the condition can be accomplished by careful questioning concerning the details of each symptom.

1. Shortness of breath. Ask the patient to show how he breathes when he is short of breath. The neurotic person will often take one deep sigh and say: "I can't get my breath all the way down," whereas the patient whose dyspnea is caused by cardiac insufficiency will breathe rapidly, deeply and regularly when his exercise tolerance is exceeded.

2. Palpitation. Ask the patient to tap on the arm of his chair to show the rate and rhythm of his heart when he experiences "palpitation." The neurotic person will tap regularly at a rate of approximately 90 to 110 a minute. The person with extrasystoles will indicate his arrhythmia with a pause every now and then. Paroxysmal tachycardia will be indicated by a very rapid regular tapping, about 160 a minute. Paroxysmal fibrillation will be indicated by rapid irregular tapping. Heart block will be indicated by slow regular thumping.

3. Pain in the chest. Ask the patient to show exactly where the pain is located. The neurotic person will point to the region of the cardiac apex with the left hand. The patient with angina of effort will point to the sternum and will often indicate the location by means of both hands. There are exceptions, but a sternal pain should be considered of true coronary origin until proved otherwise, whereas an apical pain should be considered of some other origin until proved otherwise.

Finally, it must be emphasized that the absence of objective evidence of heart disease is not a sign that the patient's complaints are psychologically induced. I have seen persons with a heart of normal size, normal auscultatory and fluoroscopic signs and a normal electrocardiogram who had typical angina of effort. When such a patient is carrying a heavy psychologic load and has a superimposed cardiac neurosis the diagnosis may be extremely difficult. However, the location

and character of the pain, its relation to effort and its relief by rest are the significant criteria. The history is of primary importance. The physical and instrumental examinations are not to be depended on implicitly.

Dr. Joseph Vander Veer: Psychosomatic relations are extremely frequent in the cardiovascular field, as Dr. Yaskin and Dr. Wood have ably pointed out. The patients an internist sees can be roughly divided into three groups.

1. Psychoneurotic patients. These patients have no organic heart disease, but exhibit a great variety of symptoms, as exemplified by the cases presented.

2. Patients with mild organic heart disease and psychoneurotic manifestations. Persons in this group may present various anxieties and worries which aggravate the condition and make them difficult to manage. The patient with hypertension who, having been told of his high blood pressure, becomes greatly concerned over his condition is an example.

3. Patients with severe organic heart disease who manifest psychotic symptoms during marked failure of the heart and patients with toxic manifestations and psychoses occurring at times as a result of mild cardiac failure associated with organic vascular disease of the brain.

Dr. Yaskin emphasized cases of patients belonging to the first group. Such cases are extremely frequent.

It is imperative to rule out organic disease. However, too often the patient is put to great expenditure of time, effort and money, when actually the manifestations described in the history are typical of neurosis and not of cardiovascular disease.

Localization of pain and tenderness over the heart itself or lateral to it is not common in organic cardiac disease, but is seen frequently in neuroses. Many other symptoms and signs suggest a neurosis rather than organic cardiovascular disease.

A patient may be much relieved to know that he has no heart disease, but he may still have his symptoms. The condition may not be merely one of weak adjustment or of a poor physical status, but may represent a much deeper disturbance.

Dr. Joseph C. Yaskin: This is an unusual meeting, in which have been presented the neuropsychiatric and the clinical points of view.

Neuropsychiatrists must at all times remain internists, not only in print but in actual, everyday practice. They are aware of some of the tricks Dr. Wood mentioned, and most carry thermometers.

If a superficial approach to a problem can straighten out a situational difficulty, I believe the case belongs to the everyday physician. However, most patients suffering from a severe neurosis with the various manifestations, whether predominantly cardiac, gastrointestinal or respiratory, are not amenable to the correction of situational difficulties. For such patients a special approach is necessary, just as such an approach is required in treatment of cardiovascular disease. The situation takes a specialist. Merely to tell a patient, "You are neurotic," does not solve the problem in the majority of cases of severe neuroses.

Dr. Morris W. Brody: It is my impression that thirty years ago such a meeting as this would not have taken place, and there probably would have been less need for it. In recent times tremendous emphasis has been placed on physical health. Popular enlightenment concerning symptoms in disease has caused a definite change in the form of mental sickness encountered. The textbook picture of major hysteria rooted in the Victorian days is rarely seen. Emotional problems today manifest themselves most commonly in terms of physical complaints.

To my mind "psychosomatic" is a poor term, for it emphasizes psyche and soma, an undesirable distinction. The physician is interested in the individual, the total organism, a human being in his environment. The modern psychiatrist has come closer to envisaging this broad aspect of medicine than any of his colleagues. In this respect the modern psychiatrist has retained something of the attitude of the country physician of thirty years ago, while the type of psychiatrist

of thirty years ago, who used fancy terms to talk about the mind (not the patient) is disappearing.

Previously the diagnosis of a neurosis was established on the grounds that the results of laboratory and physical examinations were negative. Today the diagnosis is made not by exclusion but by positive demonstration of an emotional disturbance and its relation to mental, physical and social dysfunction. In many instances it is deemed wise to institute immediate psychiatric treatment and defer temporarily detailed studies for organic disease. It is never a question of whether the patient has organic disease or whether he has an emotional problem. It is always a question of a sick person who needs help and of what physician is best equipped to give this help.

Dr. Tuft's remark that he is not impressed with the importance of emotional elements in asthma since one can expose a patient to a pollen during any season and induce asthma proves little. It implies merely that because of the direct relation between the exposure to a pollen and the onset of the asthma the pollen is the strongly causative agent and other factors are relatively less important. It is unquestioned that other persons when exposed to certain emotional situations can likewise respond with an asthmatic attack.

Medicine deals with the treatment of disease. It is unfortunate that there was a need to introduce the term "psychosomatic medicine" to remind one that emotional difficulties are also a disease.

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## ILLINOIS PSYCHIATRIC SOCIETY

CHARLES F. READ, *President, in the Chair*

*Regular Meeting, Dec. 5, 1940*

**A Possible Paternal Factor in the Etiology of Mongolism.** DR. SAMUEL J. LIPNITZSKY, Dixon, Ill., and DR. BENJAMIN BOSHES, Chicago.

A review of the literature indicates that a maternal factor has been stressed as the important agent in the production of mongolism. The paternal factor is rarely, if ever, mentioned. The role of the male parent is considered in 2 instances of mongolism which we report from the Dixon State Hospital. The white male and female infants were first cousins, and their respective fathers were brothers. No history of mongolism in the family of the parents is known. To our knowledge, no such cases have as yet been recorded in the medical literature. We therefore submit our observation of a possible paternal factor in the production of mongolism.

**Ego Management in the Treatment of a Psychotic Patient.** DR. SYLVIA ALLEN, Topeka, Kan.

This report is a brief description of a year's work with a modified psychoanalytic technic in the treatment of a schizophrenic woman of 30. The object of the treatment was to bring the patient to a status suitable for analytic work.

With the analyst serving as ego for the patient and permitting a free interplay between the patient's unbridled impulses and that which she could sense of the unconscious of the analyst, the transference-countertransference relation which evolved is described as it occurred, in fairly consistent but prelogical steps in the patient's efforts at ego formation. The process of identification seemed to be that of the usual childhood method of incorporation and projection, a "growing alongside of the analyst," as an infant does with its parents, rather than the typical identification of the psychoneurotic patient as a defense. Thus, gaining a body ego or body awareness, the patient progressed through an infantile oral stage, and

then through toilet difficulties, finally giving a fairly clear picture of adolescence in her symbolic language. The symbolic manner of speaking gave way to a much more lucid one as the two person relationship evolved into a three person Oedipus one. Her animistic concepts evolved to a point of separating moving, living objects from stationary ones.

Numerous defensive measures accompanied these transitions, with new and transient symptom formation. Increasing sublimatory activities were slow in coming, but interest broadened. Consistent efforts to produce conversion symptoms have been partially successful. The syndrome picture which resulted was that of a very sick, hysterical person.

DR. THOMAS M. FRENCH, Chicago: Dr. Allen has attempted a difficult task. It is not always so hard to understand the productions of a schizophrenic patient when one has a long time and can study a case history at leisure, but to sense what such a patient is driving at while one is sitting face to face with her is, I must say from personal experience, an exceedingly difficult task. This is, of course, particularly so when the patient's productions are as scattered as this patient's were and when they give relatively few clues at the time as to just what she is referring to.

There are two sorts of difficulties in working with schizophrenic patients. The first is an intellectual one. As I have just pointed out, it is often hard to understand just what the schizophrenic patient is trying to say. But difficulties in dealing with schizophrenic patients are not merely intellectual. Dr. Allen rightly stresses the importance of the extreme sensitiveness of the schizophrenic patient to even the most subtle changes in attitude of the therapeutist and insists that it is therefore necessary that the psychiatrist should also be exceedingly sensitive to the patient's reactions and adjust his behavior accordingly. As an illustration of this point, I recall a paranoid patient who consulted me concerning an erotomania involving one of her husband's best friends. She was fairly communicative, and we went into the problem carefully. At the end of the first hour I had exceedingly good rapport with her, but after the hour I began wondering: "Can this patient be treated outside a hospital? Am I not getting in too deep?" I began to be a little reluctant about continuing work with her. When the patient returned she apparently immediately reacted to the reluctance that I was feeling, in spite of the fact that I, of course, said nothing to her about it. She seemed to have sensed something subtle in my manner, and the rapport was gone. In view of this extreme sensitiveness of the schizophrenic patient to subtle changes in the attitude of the physician, the therapeutic task is not a simple one. It is not easy to withstand the impact of violent emotions and intense and urgent demands that are always latent in the schizophrenic patient and still maintain a therapeutic attitude. The psychiatrist may shrink from this task in several ways. His fear of an intense emotional situation may lead him to avoid dealing with the patient's real conflict, or, if the emotional discharge occurs, he may find it difficult not to be irritated or frightened by it or to escape from a certain rigidity of behavior arising out of the fear of becoming irritated. Indeed, this requires, in my opinion, a higher degree of emotional maturity than any other type of psychotherapeutic work.

DR. SYLVIA ALLEN: I have had fourteen months with this patient. I do not believe that she will gain easy access to general living, but I have sincere hopes for her pleasurable living, with the sublimation of talents as her main outlet. She is extremely artistic. I undertook the modified psychoanalysis of this patient at the request of the family. It is a formative thing for me; I am feeling my way step by step, but it offers the one hope for her recovery. The history would indicate that she has more ego than would appear from her present status, and this may be regained as she has increased confidence in me.

I allow this woman to love me when she wishes to. Perhaps it is best to have a woman psychiatrist for psychotic women patients. Of course, she does not often express her affection for me directly. She feels afraid, but I occasionally take her hand or put my arm around her shoulder. One day, in a specially seductive

mood, while lying in bed she pleaded with me to get in with her. I sat beside her, patted her a few moments and told her that this would not be unpleasant but that I knew she wanted me to go on being her physician and to help her get better.

As Dr. French has stated, this kind of work requires a great deal of libido from the analyst and quick decisions. At present the need for quick decisions and knowledge of what is going on has been manifested to me by a manic-depressive patient who lives in multiple identifications with numerous persons. If I am aware of the character she is playing I can follow. It is the first time that she has found any one whom she cannot outwit. Her need is to find some one cleverer than herself. She was able to dupe her family. With the patient on whom I reported today this factor is important, but in a much more subtle fashion. It seems to have been the thing that has made the modified analytic procedure possible with both of them.

**Hypnotic Treatment of Acute Hysterical Depression: Report of a Case.**

Dr. Milton H. Erickson, Eloise, Mich.

(A brief description is given of an experimental therapeutic hypnotic procedure, by means of which an inaccessible, unapproachable patient was manipulated psychologically without the patient's conscious knowledge, desire or cooperation. Furthermore, no effort was made to deal with the patient's illness directly, or even to recognize the fact of her illness. Instead, an approach was made only to the remote psychologic background of that illness, and the patient's tendencies and immediate need to deny, to repress and to avoid all ideas, emotions and insight relating to her problem were aided and abetted by the experimental procedure.

The case was that of a 23 year old woman in whom an acute hysterical depression developed on a proposal of marriage. Treatment by a psychiatrist and, subsequently, by a psychoanalyst had failed, and commitment seemed imperative. She was referred for hypnotic therapy, and by a detailed technic she was hypnotized, with production of a series of trance states in which she "regressed to her childhood," or was questioned about her childhood in the ordinary hypnotic trance, with waking intervals to permit a slow, gradual development of insights and understandings relating particularly to the sexual instruction she had received as a small child. After three hypnotic sessions of four hours each, the patient acquired an adequate background of insight into the character of her sexual instruction in childhood and the nature of her present hysterical problem, with consequent recovery and successful marital adjustment over a period of years. Many theoretic questions concerning the precise role and the significance of the forces dealt with in psychotherapy, especially the relative values of the conscious and the unconscious processes and insights, are discussed.)

DISCUSSION

Dr. Jules H. Masserman, Chicago: Although it is often futile to cavil at vague nosologic distinctions, I believe that in the present instance it is important to emphasize, with Dr. Erickson, that he was dealing not with a true psychotic melancholia, but with a chronically neurotic personality which exhibited an acute hysterical reaction with marked organic dysfunctions and only a few depressive features. The differentiation, even in the absence of a detailed history, may be made on a number of counts, the most important of which are the patient's early maternal fixations, her lack of emancipation and maturity in occupational and social adjustments, her genital inhibitions and her tendency to acquire recurrent, severe and symbolically appropriate somatic symptoms under specific emotional stresses. In this connection, also, the patient's development of a rather too typical "psychosis" after only a few months of contact with depressed patients at the Eloise Hospital and her acceptance of indirect hypnosis in themselves indicate that she was suggestible to a degree which, by an old criterion of Babinski's, would also speak for marked hysterical tendencies. In view of the patient's

retained emotional pliancy and the absence of depressive withdrawal, it is not surprising that Dr. Erickson was able to obtain a rapport and secure therapeutic results that would not have been possible had the patient actually been in a rigid, narcissistically isolated, implacable melancholia.

Dr. Erickson has given an excellent illustration of a specialized technic of hypnotic treatment, for which he implies a certain degree of originality and specificity. I believe it is important to point out, however, that he has utilized only in a special way many of the principles applicable to all successful psychotherapy—analytic, suggestive or otherwise. To wit:

1. He first induced the patient to submit to treatment by the indirect, but technically important, steps of (*a*) assuming sufficient initiative to break through the patient's primary libidinal inertia, (*b*) circumventing her initial distrust of the therapy by a flanking approach through an available ally, in this case the patient's girl friend, (*c*) purposely making his introductory contacts sufficiently warm, reassuring and friendly to induce a desire on the part of the patient for further interpersonal relations and (*d*) promising, not so much in words but by eloquent implication and by the direct example of her roommate, that the patient had much to gain (and nothing of real value to lose) by following the physician's guidance, even though this might mean abandoning certain cherished libidinal positions and relinquishing some of the secondary gains her neurosis had brought her. Any therapeutist who neglects these essential preliminaries of treatment, either by employing a crudely pseudoanalytic "passive" technic or by exhibiting a tactless furor to break through the patient's carefully built up resistances and get at his "complexes," will either lose the patient outright or else so accentuate his anxiety and reactive defenses as to prejudice all further progress.

2. Within the temporary framework of the psychotherapeutic field thus established, Dr. Erickson's next step was to foster a deeper and more specific interpersonal relation with his patient, that is, one in which he would play the role of a parental surrogate, and thus become endowed with sufficient emotional cathexis and symbolic authority to influence the patient's childhood fixations and attitudes. Dr. Erickson's special technic was to use explicit, hypnotically reenforced suggestion that he actually be regarded as the patient's mother, but in principle his procedure was really no different than that adopted by any therapeutist who, by the conscious or unconscious assumption of a kindly, reassuring, protective and yet directive attitude, implicitly functions as the idealized mother who is so avidly sought by the harried, insecure, regressive neurotic patient. In technical terms, then, Dr. Erickson, by a transference identification, secured a manipulative purchase on the patient's ego through which he could then influence previously inaccessible unconscious dynamisms.

3. The third step in Dr. Erickson's therapy was to use the power and authority with which he was now invested to elicit and allay the deep unconscious guilts and resolve the pathologic conflicts that had overwhelmed the patient's psyche. In doing this, he skilfully employed a modus operandi the existence of which is denied by some analysts, and yet which is commonly and successfully used in many forms of briefer psychotherapy. The method consists essentially of (*a*) the formation of an implicit, unspoken, but nevertheless effective, understanding between the patient and the therapeutist, (*b*) the specific avoidance of the necessity for verbal expressions of guilt-charged material by the patient until it had been sufficiently relieved of cathectic anxiety by anticipatory permissive and forgiving reassurances and (*c*) the elicitation of verbalized "insight" only in such doses and at such intervals as are indicated by the capacity of the patient's ego for acceptance, assimilation, integration and readjustment.

It will be noted that this technic differs from so-called distributive analysis in that, in conformity with the demands of briefer psychotherapy, it avoids unnecessary, premature and possibly disruptive verbalizations and yet deals with the unconscious conflicts actively, specifically and at a carefully governed tempo. Moreover, the therapeutist does not hesitate to use every influence the transference

affords not only to relieve anxiety by a partial discharge of repressed material, but also to encourage more acceptable ego defenses and to relax the severity of the neurotic superego through new and healthier identifications. Such a technic, of course, cannot explore the patient's unconscious exhaustively, nor can it, because of the patient's strong defenses, bring many of the patient's conflicts directly into consciousness; in this connection, Dr. Erickson's directions to his patient to keep the procedure unconscious was, in a sense, supererogatory. Nevertheless, such psychoanalytically oriented, brief psychotherapy not only meets the limitations of time and effort imposed by the necessities of practice and the clinic, but, as Dr. Hugh T. Carmichael and I have shown elsewhere, may be highly effective in the treatment of acute neurotic problems of persons who have retained a relatively good capacity for emotional reintegration.

4. Dr. Erickson's final step in the treatment was to utilize the momentum of the therapy, his enhanced transference authority and the patient's new-found, but still partial and precarious, relief from excessive inhibitions in order to secure a favorable change in her social adjustments, namely, a trial of marriage. In the same way, a patient who under analysis has discovered the roots of a phobia may be directly encouraged to assert his mastery of it in his daily behavior. I think all would agree with Dr. Erickson that newly won insights are often better crystallized and retained by trial and success readjustments in real life than by endless reiterations of merely verbal formulas on the part of either the patient or the physician.

But now the question presents itself: If these broad principles of psychotherapy are followed, is it really necessary to employ the difficult, specialized and possibly precarious methods of hypnotism? Could not Dr. Erickson have dispensed with the symbolic aura of mystic omniscience and omnipotence created in the hypnotic sessions and, instead, utilized his understanding and skilful suggestive technic to produce equally good results with the patient in the waking state? Does not the fact that the patient so readily accepted indirect hypnosis indicate that, in her guilt and anxiety, she was ready to receive ego-syntonic guidance if properly offered in any sufficiently disguised and acceptable form? For that matter, is the material she produced in the so-called trances really of much more intrinsic significance than that she was in rapport with the hypnotist and therefore obligingly produced screen memories that she considered appropriate? Particularly to illustrate the latter point, I should like to cite an anecdote.

Some ten years ago I was presented with what seemed to be an excellent opportunity to demonstrate to a class of medical students the technic of eliciting repressed memories by means of deep hypnosis. The hypnotic subject was an intelligent college girl—a student of biology—whom I was treating for an organ neurosis and who had a currently strong positive transference to me. After inducing a deep hypnotic trance and demonstrating the various phenomena of amnesia and analgesia, I confused her orientation for place and time by the usual technic, suggested to her that she was now reliving her sixth birthday and then directed her to describe the scene about her. In a childish voice and with appropriate gestures, she proceeded to give a wealth of detail as to the place of her birthday party, her own dress and hair ribbons, the identity of her playmates, etc. Encouraged by this seeming success, I then instructed her, after the proper preparation, to give a current description of her fourth and then her second birthday party, and both times apparently secured an eyewitness account of the scene and of her experiences on each occasion. To pursue this investigation of what seemed to be a highly unusual subject, I then directed her actually to relive her birth and received the halting, tortured but amazing reply, "I feel cramped! . . . Now it is cold!" followed by a neonatal cry! Thoroughly suspicious by now, I then told her in a matter-of-fact, authoritative voice that she was now in her eighth month of intrauterine life, but that she nevertheless would be able to describe her sensations. As anticipated, the patient again responded, this time with but the simple statement: "It throbs!" All too apparent, then, was the true

state of affairs: The patient, in accordance with an intense transference-determined desire to comply with my wishes that she produce "repressed" material, had unconsciously culled from her knowledge of embryology an impossible screen memory that she thought appropriate. This and similar experiences have demonstrated to me the usefulness of a cogent maxim: "It is a wise hypnotist who is continually aware of just who is hypnotizing whom!"

This brings me to the final point in my discussion: the probable psychodynamic formulation of the neurosis in Dr. Erickson's' patient. During the past several years, Dr. Henry Brosin and I have been interested in the psychiatric and psychoanalytic investigation of cases of anorexia and neurotic vomiting in young women and have been repeatedly impressed with a fundamental emotional pattern in these cases. Briefly, the essential formula is this: (*a*) an intense early fixation on the mother; (*b*) an abortive attempt to shift to passive oral dependence on the father; (*c*) thwarting of this desire by the mother; (*d*) extreme guilt over the cannibalistic fantasy of the father's symbolic retention by oral incorporation, and (*e*) subsequent oral or anal restitution by vomiting or diarrhea whenever threatened by a similar relation to a father surrogate in later life. I should, therefore, agree with one of Dr. Erickson's last suggestions—that his patient's most disturbing conflicts were not primarily in the genital sphere, but were concerned with an impending, but forbidden, oral-incorporative dependence on her prospective husband—a threat to which she first reacted with self-denying vomiting and from which she then fled in panic to Dr. Erickson's protection as a forgiving mother imago. However, when Dr. Erickson avoided a direct exploration of this fundamental conflict, received her with forgiving maternal protection, talked in acceptable genital instead of anxiety-cathected oral terms and finally gave her, by virtue of his transference authority, partly explicit and partly implicit permission to transfer her dependence from her mother through him to a husband, she summoned up just sufficient courage to try that experiment and to benefit through its success—an outcome probably in no small part due to the indulgent, forgiving, essentially maternal attitude also adopted by her fiance. In effect, then, Dr. Erickson's role in the therapy was to displace the patient's verbalizations to her relatively amenable genital problems while concurrently allaying her deeper and more cogent oral anxieties—in part by the mystic magic of his hypnotism, but mainly by his pervadingly forgiving, permissive, encouraging attitude and by the immediate consolidation of all therapeutic gains by successful adjustments to real life.

Dr. Maxwell Gitelson, Chicago: I had a patient some time ago who reported that in his childhood he had a very nice way of "getting away with murder" with his mother, who was quite willing to let him do so. This concerned the patient's aggressions toward a younger sister, to whom the mother was rather hostile also. The patient's method was to hit the sister with something, his hand or a missile of some sort, and then to explain that his "hand had slipped." The mother would accept the explanation. It seems to me that in the case presented by Dr. Erickson there was a similar situation in which the patient was ready to be corrupted, as was the mother in my case. Dr. Erickson's therapeutic situation, in its essentials, was a seductive one, in which the patient collaborated. Dr. Allen, earlier in the evening, spoke of how completely aware a patient is of the essential situation in a relationship with other human beings. It is hard to believe that Dr. Erickson's patient could have been so completely fooled as to think that she was acting as a chaperone. It is my impression that Dr. Erickson was identified not with the patient's mother but with the patient's lover. I was struck by the statement that the lover had first noticed the girl's receptiveness toward him, after which he had responded to her. In other words, she must have been compliant to his advances. In the treatment the sexuality that she craved was made acceptable to her by the fact that she was able to allow the corruption of her established standards of conduct. These factors are important,

it seems to me, even in the face of the fact that the problem is not really a sexual conflict, but a deeper, pregenital one, as Dr. Masserman stated.

DR. CHARLES F. READ, Elgin, Ill.: I should like to ask what was the procedure, the attitude, perhaps the experience and technic of the psychiatrists who previously treated this patient.

DR. MILTON H. ERICKSON: In reply to the question which concerned the possibility of having accomplished similar therapeutic results by holding two or three psychiatric interviews with the patient: The psychiatrist, a straightforward, sensible, forthright medical man, treated the patient daily for a period of weeks in direct, unpretentious, common-sense psychiatric fashion. The only result was that the depression deepened. Then, because this capable psychiatrist failed, the family insisted on another attempt, and so she was sent to a psychoanalyst. When this failed she was sent to me.

I am confused myself concerning the role I played with the patient. I feel that I played a number of roles, which would include those of a father, a mother and various other figures.

As to the duration of each interview, on each of the three occasions the interview began at 1 p. m. and the patient was dismissed by 5 p. m. Much of the time of the interview was spent in manipulating the patient psychologically from one mental state to another.

Dr. Masserman raised the question whether I could have dispensed with the attitude of mystic omniscience associated with the hypnosis. I looked on the entire situation as an experimental and not as a therapeutic situation. By so regarding it, I had the opportunity of carrying on an experiment in psychotherapy without the usual recourse to verbal exploration, and hence this attitude of omniscience was significantly useful. The primary problem seemed to me to be that of devising a situation in which the patient could meet her current problem without becoming frightened or discouraged.

Dr. Masserman spoke of the patient who relived her eighth month in her mother's womb. I do not like to embarrass Dr. Masserman in any way; I admit I had the same sort of experience in causing patients to regress to an earlier period of their lives until I learned an adequate and reasonable technic and became fully aware of the fact that in the earlier stages of life there is no language ability. Hence, the hypnotist, in causing the patient to regress to the earlier stage, must rely on measures other than language. Yet, regrettably, one hears of hypnotists inducing a state of regression in a subject to a very early stage of his life and then carrying on remarkably learned conversations with the subject, unmindful of the fact that, if a state of regression had been elicited, the subject would not and could not understand. Furthermore, if there did exist a state of regression, the subject really could not speak to the hypnotist, since he had not yet met the hypnotist and would not for many years. When cognizance is taken of these important facts in the regression of a subject, one is still confronted with extreme difficulty in inducing a state of regression and yet maintaining hypnotic contact with the patient. There is need, if contact is to be maintained with the subject during regression, for the hypnotist to identify himself with some person actually belonging to that period of the patient's life to which he has regressed. When this is done, with careful attention to all details of psychologic technic, then one can secure a genuine regression and not the type Dr. Masserman so rightly criticizes and which so many others assume to be an actual regression.

**Prognostic Value of Intravenous Administration of Sodium Amytal in Cases of Schizophrenia.** DR. JACQUES S. GOTTLIEB and DR. JUSTIN M. HOPE, Iowa City.

This paper is published in full in this issue of the ARCHIVES, page 86.

## PHILADELPHIA COLLEGE OF PHYSICIANS, SECTION ON OPHTHALMOLOGY, AND PHILADELPHIA NEUROLOGICAL SOCIETY

FRANCIS HEED ADLER, M.D., *Presiding*

*Joint Meeting, Dec. 19, 1940*

**Adie's Syndrome: Report of a Case.** DR. THOMAS H. COWAN.

A case of Adie's syndrome, with tonic reactions of the muscles of the iris and ciliary body, is presented.

J. K., a man aged 31, was first seen in September 1940. He complained of poor distant vision and desired refraction. On questioning he stated that he was and had been in excellent general health, with no neurologic complaints, past or present, and no history of syphilis, tuberculosis or other condition.

Ocular examination showed that the right pupil was larger than the left and was slightly flattened above. There was little or no reaction of the right pupil to light when tested by the usual method of flashing a light into the eye. The consensual reflex was also absent. However, on prolonged exposure to light, that is, for several minutes, a slight reaction was noted. After removal of the stimulus, the pupil slowly dilated. The direct and consensual reflexes of the left eye were prompt and normal in amplitude.

In accommodation the right pupil reacted well after a short delay, and in the strongest accommodation it contracted even more markedly than the left, the measurements of the two being 2.5 and 3.5 mm., respectively, at the near point of accommodation. When the accommodation was relaxed, the right pupil remained small for some moments and then slowly dilated to its former size. The reactions of the left pupil during accommodation seemed entirely normal.

On measuring the accommodation, it was found that the right eye possessed 12 D., with a near point of about 8 cm., while the left eye had only 9 D., with a near point of 11 cm. Furthermore, in the right eye a spastic condition of the ciliary muscle, similar to that in the iris, was found, for the near point of 8 cm. was achieved much more slowly than the near point of the left eye and immediately on removing the stimulus for accommodation vision for distant objects was blurred in the right eye but slowly became clear again.

Accommodation in the left eye, however, occurred in a normal manner.

With 5 instillations of a 4 per cent solution of homatropine hydrobromide, administered at fifteen minute intervals, the size of the right pupil was 5 mm. and that of the left 6 mm. Refraction gave the following results:

Right eye: —1.50 D. sph. —3.00 D. cyl., axis 20; resulting vision 6/6 +.

Left eye: —2.00 D. sph. —2.50 D. cyl., axis 160; resulting vision 6/6 +.

This prescription was ordered full and was worn by the patient in comfort for both near and distant vision, in spite of the bizarre accommodative behavior.

The patellar reflexes could not be elicited. The patient stated that they had never been present. He also said that the difference in size of the pupils had been present as long as he could remember.

**Multiple Sclerosis as an Ophthalmoneurologic Condition.** DR. WALTER I. LILLIE.

Multiple sclerosis is a rare disease characterized by intermittent involvement of the central nervous system, producing motor or sensory disturbances, most common of which are those affecting the extremities, and visual disturbances, such as diplopia, nystagmus and retrobulbar and optic neuritis. Contrary to descriptions in textbooks, retrobulbar and optic neuritis are among the earliest and most characteristic episodes in the course of this disease. Of 500 definitely

proved cases of multiple sclerosis, visual disturbance was the presenting symptom in 15 per cent; in an additional 40 per cent visual manifestations represented the second or third episode in the course of the disease. Ophthalmologically, one finds diminished vision, normal fundi and central scotoma associated with the acute retrobulbar neuritis of multiple sclerosis. In cases of severe retrobulbar neuritis the central scotoma may extend to the periphery, or even produce complete loss of vision. Pallor of the disk is a later sign. Optic neuritis differs from retrobulbar neuritis in that the inflammatory process is at the optic disk and is visible with the ophthalmoscope. The prognosis for improvement is better for retrobulbar than for optic neuritis. The more common type of retrobulbar neuritis is acute, with sudden loss of vision, but there is also a chronic form, with insidious loss of vision.

The significance of retrobulbar neuritis is not thoroughly appreciated, as evidenced by confusion in the literature and by the fact that most of the patients have been subjected to unwarranted types of therapy. It is imperative that such patients have complete general and neurologic examinations, including analysis of the spinal fluid. In addition to multiple sclerosis, the clinical syndrome of retrobulbar neuritis may be due to meningoencephalitis; basofrontal tumor; diabetes; pernicious anemia; leukemia; poisoning due to nicotine, alcohol, heavy metals and chemicals; lactation; sinusitis, and hereditary diseases.

The prognosis in retrobulbar neuritis is good, and most patients would recover without treatment. This accounts for the unwarranted enthusiasm of the exponents of the various types of therapy, particularly intranasal surgical procedures. My experience has been that sinusitis rarely, if ever, produces retrobulbar neuritis. Complete studies by various consultants produces the best diagnostic and therapeutic results. Foreign protein therapy and pilocarpine sweating have proved of benefit in shortening the course of the disease and in minimizing the residual functional impairment of the visual apparatus.

DISCUSSION

DR. MANUEL SALL: Retrobulbar neuritis as an early or associated symptom of multiple sclerosis is not uncommon. The syndrome tends to occur early rather than late in the course of the disease and is usually unilateral. Some idea as to its frequency may be obtained from the following figures: In a total of 88 cases of retrobulbar neuritis reported by Fleischer, Marburg and Weil, signs and symptoms of multiple sclerosis were presented. Adie, who studied 70 cases of acute retrobulbar neuritis during the first week of the illness, found that signs of multiple sclerosis were present in 31. It might be expected that more patients would have shown evidence of multiple sclerosis had they been followed further. The figure obtained by Sachs and Friedman, in 1921, for the incidence of retrobulbar neuritis in cases of multiple sclerosis seems rather low. Of 141 cases of multiple sclerosis, they found temporal pallor in 46, in 11 of which there was optic neuritis. They made no mention of having performed studies of the visual fields or of visual acuity in this series. The visual fields and visual acuity are of far greater diagnostic import in the recognition of retrobulbar neuritis than the appearance of the fundus and the pallor of the disks. The interval from the time of appearance of the optic neuritis to that of other associated signs of multiple sclerosis is usually not long. However, some rather rare cases have been reported, particularly that by Kinnier Wilson of a woman aged 21 who presented a picture of retrobulbar neuritis but no other symptoms for twenty-one years, when spastic paraplegia and other signs of multiple sclerosis developed. It might be interesting to mention that nystagmus, quite the commonest symptom in multiple sclerosis, occurs in over three fourths of the cases. So-called jelly nystagmus, described by Paton, is observed through the ophthalmoscope as a minute, rapid movement of the eyeball and is supposedly pathognomonic of multiple sclerosis. It occurs infrequently. The Argyll Robertson pupil is rare, as are pupillary differences

and irregularities. From the point of view of the neurologist, it is interesting to note that the presence of lesions immediately behind the nerve head may give rise to edema of the disk that is hardly distinguishable from the true papilledema of increased intracranial pressure. The question of tumor of the brain presents itself in these cases. However, the fact that visual impairment has preceded the change in the fundi, the tendency of the edema to clear up rapidly and the absence of other evidence of increased intracranial pressure will exclude the diagnosis of tumor.

DR. JOSEPH C. YASKIN: Dr. Lillie has raised the important question of the relation of retrobulbar neuritis to multiple sclerosis. There can be no disagreement that the commonest cause of retrobulbar neuritis is multiple sclerosis. He brought up the problem of the advisability of examining and operating on the sinuses in cases of acute retrobulbar neuritis. This is an old quarrel between the rhinologist, the neurologist and the ophthalmologist. From the practical standpoint, all that is known of multiple sclerosis is a little about its pathology. Nothing is known about its pathogenesis and still less about the etiologic factors. One does not even know whether it is an inflammatory or a degenerative disease. Given, therefore, a condition in which there are a grave ocular condition and the prospects of other complications, and also the signs of clinically well marked disease of the sinuses, it has been my feeling and that of my associates that the sinuses should receive appropriate attention. I should like to stress the fact that the mere roentgenographic evidence of a thickened mucosa is not sufficient justification for the opening of the posterior sinuses, but if the rhinologist finds free pus in these sinuses, it is my feeling that in the presence of retrobulbar neuritis the patient should be given the benefit of surgical treatment. Perhaps this is the focus that is responsible for the multiple sclerosis. Is it not possible that the cleaning out of these sinuses will delay the development of further complications for some time at least?

DR. MAXWELL LANGDON: Dr. Lillie was on firm ground when he stressed the need of thorough and complete study of any cases of retrobulbar neuritis which one may see. It is difficult sometimes to put one's finger on the etiologic factor, and only by consideration of all the possibilities may one in any way be sure of arriving at a just conclusion. Dr. Yaskin said that undoubtedly multiple sclerosis is the chief cause of retrobulbar neuritis. Apparently, he thinks that the great majority of the cases of retrobulbar neuritis are those associated with multiple sclerosis. I am not sure that that is correct. I think that when the cases of toxic amblyopia are considered, this condition will be found almost equally important in the production of retrobulbar neuritis. Of course, the neurologist and the ophthalmologist attack the problem from distinctly different angles. The neurologist is interested in the multiple sclerosis; the retrobulbar neuritis is merely a phase, a part of the general picture, whereas the ophthalmologist takes the retrobulbar neuritis as his primary problem and asks what is causing it. I think, therefore, that the neurologist would see more cases in which retrobulbar neuritis accompanied multiple sclerosis than any other condition. He would not see as many cases in which toxic amblyopia was the cause. That may be one reason it seems to some neurologists that multiple sclerosis is a predominant factor in the production of retrobulbar neuritis. Dr. Yaskin also referred to the possibility of the sinal condition causing retrobulbar neuritis. If retrobulbar neuritis is caused by sinal disease, it is in a very small percentage of cases, possibly in only a fraction of 1 per cent. I do not agree with Dr. Yaskin that the sinuses should not be invaded unless, I think he said, free pus is found. In my experience, the cases of sinusitis which cause ocular disease are not those in which free pus is present. There is a low grade hyperplastic inflammation of the sinuses in such cases, and it is difficult for the rhinologist to be sure of the presence of the active sinusitis.

DR. FRANCIS H. ADLER: There are two curious things about multiple sclerosis. One is the predisposition of this disease to affect such a localized part of the ocular pathways when it has a widespread and diffuse distribution in the central nervous system. Every one agrees that multiple sclerosis singles out the papillomacular bundle in the optic nerve. The second point of interest is that in nearly all the cases, even when the disease is subsequently proved to be multiple sclerosis, improvement follows opening the sinuses. It seems possible that some day it will be shown that opening the sinuses does more than merely drain them. It may well be that such an operation in some way affects reflex control of the local blood vessels, with temporary benefit to the pathway. One should be pragmatic about treatment, and if it is found that opening the sinuses helps, they should be opened.

DR. WALTER I. LILLIE: I knew my pointed statements concerning sinusitis as an infrequent cause of retrobulbar neuritis would stimulate discussion. For the past fifteen to twenty years operations on the sinuses have been instituted frequently for relief of acute retrobulbar neuritis, even when clinical and roentgenologic examination revealed little or no pathologic damage. The clinical term "hyperplastic" was given to this type of sinusitis to differentiate it from the classic purulent sinusitis. The treatment of acute retrobulbar neuritis is not specific, and many methods are employed. Fortunately for the patient, the course of acute retrobulbar neuritis is self limiting, persisting usually for ten days to six weeks. The prognosis for return of normal vision and visual fields is excellent, as only 2 per cent of patients have a permanent visual defect. When this occurs, I believe the optic nerve is affected in the bony optic canal, with resultant swelling of the nerve and early damage due to pressure. This can be compared with Bell's palsy; when the facial nerve is involved in the bony facial canal, permanent damage is the result. In 98 per cent of the cases of acute retrobulbar neuritis, vision returns to normal regardless of the treatment employed. One can remove an appendix, a big toe or the tonsils, aerate the sinuses or treat the posterior orbit with roentgen rays, as reported recently in the French literature, and, regardless of the method, improvement will occur. My own experience with sinusitis as a causative factor is on the negative side. I once examined 200 patients with purulent or hyperplastic sinusitis, and not one had retrobulbar neuritis. All of us here, I am sure, would have to search our private and clinical case files before we could find a patient with a retrobulbar neuritis syndrome who was referred to us by a rhinologist. Dr. Adler has suggested that congestion following the operation on the sinuses might be the factor concerned with resultant improvement. The same can be said for foreign protein therapy; that is, the dilatation of the peripheral arterioles, rather than the amount of fever produced, is the probable reason for the good results.

Retrobulbar neuritis associated with multiple sclerosis usually occurs during the fall and spring, which suggests an infection or a virus as a cause. It is my opinion that surgical intervention has no proper place in the treatment of acute retrobulbar neuritis.

**Late Results of Cervical Sympathetic Resection in Cases of Retinitis Pigmentosa.** DR. FRANCIS C. GRANT.

A brief review of retinitis pigmentosa is given, and the possibility of its being due to interference with the blood supply to the retina and choroid is suggested. The sympathetic nerve supply to the eye is reviewed, and the operations proposed for denervation are outlined.

Nine cases of retinitis pigmentosa are presented. In all the "high" operation was performed, with stripping of the common internal and external carotid arteries and excision of the upper and middle cervical sympathetic ganglia and the intervening nerve trunk. Constriction of the fields, with subsequent loss of vision, seemed definitely more delayed in cases in which operation was performed than

in those in which it was not. It is questionable whether this operation is the best but it seems to be the easiest and safest. As the vertebral nerve is not sectioned, this may be a source of return of sympathetic control. Regeneration of nerves should not occur, as the operation is apparently preganglionic.

DISCUSSION

DR. EDMUND B. SPAETH: There are two or three points I can add to Dr. Grant's presentation. First, in the selection of the cases for surgical treatment, Dr. Grant and I have tried as much as possible to match each case selected with a similar one from the various clinics at our command and from our private practice, so that every operative case had as a control a nonoperative one. It is interesting that the condition has been almost as good in the controls as in some of the operative cases, but not quite as good in all. Given certain definite signs and indications, the results in some of the operative cases have been better.

Two observations are certain: The first concerns the appearance of the vessels before and after operation. After operation vessels which formerly were not present appear within the threshold visibility of the ophthalmoscope. To illustrate this point, I have made two rough sketches from one of the cases. They were made with a Gullstrand ophthalmoscope before and after the operation; each vessel was plotted on each of the nerve heads and labeled as an arteriole or a venule, and the sketch was carefully dated. From time to time, at certain intervals, the same fundus was studied thoroughly. The second sketch was made eleven months later. The new blood vessel formations were sketched in with red. In the final analysis, the change in appearance is only an arteriolar dilatation of such extent that the vessels are now within the visibility of the ophthalmoscope. These blood vessels have all been arterioles; they were never venules.

The second observation is the tremendous variability in the fields of vision for several months after the operation. Dr. Evans said, applicable to this: "The fields dilate and recede, as if the tide were washing up on the sand and then receding, and they do this for several months after the operation." With the same amount of illumination and a stimulus of the same strength, the field varies. A recession, however, is never quite as marked as it was before the dilatation, and it seems finally to become stabilized. As Dr. Grant said, we present our observations and permit you to draw your own conclusions.

DR. ISAAC TASSMAN: Dr. Grant touched on the cause of retinitis pigmentosa; I believe he said that the origin was congenital in 1 case, and unknown in the others. It is generally accepted that in most cases this disease is classified as heredofamilial and is considered to be a degeneration of the tapetoretinal type. Cases may occur in more than one member of the same family and in successive generations of that family, although not necessarily so. It would be interesting to know whether there were any other cases in the families of the patients reported on here. In other words, were the cases typical in that respect? It is assumed that the ophthalmic picture was characteristic, and it is known that the deposits of pigment usually occur at the equator. The marked narrowing and attenuation present raise the question whether this is an associated condition or the cause of the degeneration. It is reasonable to expect that, as a result of the sympathectomy, there should be improvement in vision, such as was demonstrated in these cases, but I should like to ask whether one may expect the same result in cases of retinitis pigmentosa as in cases of essential hypertension, in which there would be no pigmentary degeneration of the retina of this characteristic type.

DR. WALTER I. LILLIE: I should like to ask Dr. Spaeth, since the rationale of sympathectomy is to obtain dilatation of the peripheral arterioles, whether the retinal arterioles were measured with a graticule before and after the operation. Also, were the cases classified as to the duration of the condition or the age of the patient for the surgical choice of treatment? The best results from sympa-

thectomy for Raynaud's disease occur in those patients who show dilatation of the peripheral arterioles with intravenous injection of foreign protein.

DR. GEORGE D. GAMMON: I should like to ask Dr. Grant whether any regeneration occurs. It is well known that sympathetic fibers regenerate rather rapidly when the section is postganglionic. His operation is a somewhat limited sympathectomy of the carotid artery. From the type of operation, it is possible that he might interrupt postganglionic fibers in some cases and remove the ganglion itself in others. Might not this account for the variation in the results in different patients?

DR. FRANCIS H. ADLER: Would it not be better to carry out the operation on one side only in some cases, so that one could compare the intact with the sympathectomized side? I should like also to ask whether the peripheral operation which Dr. Grant performs gives rise to sensitization of the blood vessels to circulating epinephrine. If the operation were a central denervation, this peripheral sensitization would not occur.

DR. FRANCIS C. GRANT: I was afraid some one would ask me about the pathologic changes, as Dr. Tassman did. Duke-Elder has a complete set of notes, to which I cannot add much. That seems to be the fountainhead of knowledge. Typhoid therapy has been used as a method of treatment, but I think it has been abandoned. The number of types of treatment that have been used and abandoned is provocative. Of the two articles I found on this subject, one was in Dutch and the other in Russian.

As to Dr. Adler's question about operating on one eye and observing the other: That was done to a certain extent in our cases, for the patients were operated on at intervals of about six weeks, permitting observation and comparison. It is curious that in about one-half the cases in which operation was done on one side the effect was bilateral. Such a result is being reported by those who perform this operation. If one does a right sympathectomy, one may get a dilatation in both fields. Everybody who has done the operation has remarked on such an effect. One would have to observe the patient over three or four years to see what the difference in vision in the second eye would be. That is a possible and logical thing to do. In a way we did this, although, since we operated on the good eye and the bad eye was usually very bad, there was not much opportunity for comparison. Dr. Gammon has brought up an interesting problem with regard to the regeneration of the sympathetic nervous system and whether the procedure we use is preganglionic or postganglionic. If we are cutting the postganglionic fibers, we are perhaps making the sympathetic vessels in the retina somewhat more responsive to circulating epinephrine, as in the case of Raynaud's disease; the reason for the failure in cases of sympathectomy of the upper extremity in the past has been that the postganglionic type of the operation was carried through and, consequently, the vessels were more sensitive to the epinephrine and quasi-recurrence of the disturbance took place. Regeneration is also more likely to occur after a postganglionic operative procedure. Frankly, I am not clear whether we have done the preganglionic or the postganglionic operation. I should say that we had done the postganglionic one. If one wanted to do the preganglionic operation, one would, I think, have to use the anterior route. To my knowledge, there is not sufficient justification for a definite answer. The regression is due to two factors: regeneration and the configuration of the disease.

**Diagnostic Significance of Retraction of the Upper Lid.** DR. FRANCIS H. ADLER and DR. HAROLD SCHEIE.

Three cases of spasmodic retraction of the upper lid are reported and the diagnostic significance of the signs discussed.

This paper will be published at a later date.

DISCUSSION

Dr. Frederic Leavitt: All in neurologic practice see unusual reactions, such as Dr. Adler and Dr. Scheie have so aptly described. Recently, in the ward service of the Graduate Hospital, we observed a patient with palsy of the seventh nerve following an infection in whom a peculiar epiphora developed after regeneration of the nerve. One explanation of the phenomenon was that there may have been a wandering of nervules over the wrong pathways. I must say, on reminiscing, that I, and I am sure others, have occasionally seen the phenomenon described by Dr. Adler. Dr. Groff operated on a patient who had had a trauma to the head with resultant internal hydrocephalus in whom there developed marked spasmodic retraction of both upper lids. Dr. Groff and Dr. Spaeth both saw this patient, and Dr. Spaeth saw him again some months ago. Several years ago there was an interesting case in Dr. Burr's service at the Philadelphia Orthopaedic Hospital, that of a woman who had Addison's disease and was treated at the time by the intravenous injection of epinephrine. After each injection a pronounced retraction of each upper lid developed, which would persist for some minutes; Dr. Burr remarked at the time that she resembled a "feline" who had been suddenly irritated or scared. This condition is also seen generally bilaterally, in post-encephalitic states, as a sort of paraoculogyric crisis in which there is marked retraction of the lids without movement of the orbits. It is also seen occasionally in cases of multiple sclerosis, and it becomes almost a part of the physiognomy of that disease in some instances. I have also noted it in cases of scleroderma with involvement of the face. This condition has also been observed as a functional or physiologic complication in psychopathic patients. I have seen this phenomenon in psychotic patients in the wards of the Philadelphia Hospital, generally in association with visual hallucinosis of a terrifying nature. Dr. Adler has clearly differentiated between the sympathetic type of involvement of Müller's muscle and the more or less third nerve type of palsy of the striped or levator muscles of the upper lid.

The case reported by Dr. Grant as an instance of meningioma of the sphenoid ridge is interesting. In the Graduate Hospital have occurred a number of cases of meningioma of the sphenoid ridge, and I cannot recall having seen retraction of the lids in any of them. Would Dr. Grant let me know whether he has seen it in any other case? Dr. Adler and Dr. Scheie have presented an interesting observation, and now that one is conscious of it, one will be more on the watch for it.

Dr. Warren S. Reese: A number of years ago I presented before the section on ophthalmology of the Philadelphia College of Physicians a patient with a condition such as Dr. Adler has described. The patient, who was recovering from palsy of the third nerve, showed a definite von Graefe sign. I did not refer to this, however, as a pseudo von Graefe sign, for, so far as I could see, it was quite typical. I have also had the good fortune to see some of the cases of oculogyric crises to which Dr. Adler referred. From a clinical standpoint, the condition in these cases seemed much different, the retraction of the lids being less pronounced than that in the case of oculomotor palsy.

**The Oculomotor Nerve: Clinicoanatomic and Etiologic Considerations.** Dr. Joseph C. Yaskin.

The most common causes of paralysis of muscles supplied by the third nerve include syphilis, vascular lesions, trauma, diabetes, neoplastic processes, acute suppurative and nonsuppurative infections of the nervous system, chronic degenerative diseases, exogenous intoxications, botulism, mushroom poisoning and myasthenia gravis. An etiologic and anatomic diagnosis is at times difficult, and is often necessary for therapeutic reasons. Such a diagnosis may depend on the intimate knowledge of the course and relation of the oculomotor complex. This presenta-

tion is an attempt to discuss the various clinical types of oculomotor palsy from the standpoint of the regional distribution of the lesions, and is summarized in the accompanying tabulations.

*Intraorbital Lesions of the Third Nerve*

Intrinsic disease of muscles: abiotrophy, myopathy, thyrotoxicosis
Myasthenia gravis
Trauma
Conditions producing exophthalmos
(*a*) Originating in the orbit
(*b*) Extending by contiguity into the orbit
(*c*) Systemic and distant disturbances

*Lesions of the Third Nerve in the Region of the Cavernous Sinus, Sphenoid Fissure and Middle Cranial Fossa*

Thrombosis, phlebitis and injury of the cavernous sinus
Aneurysm
Herpes zoster
Infection of the paranasal sinuses
Tumors of the sphenoid ridge: meningioma, osteoma
Other space-taking lesions in the middle fossa

*Lesions of the Third Nerve in the Interpeduncular Space and at the Base of the Brain*

Inflammatory: acute and chronic meningitis; Weber syndrome; interpeduncular syndrome
Vascular: aneurysm; sclerosis; subarachnoid hemorrhage; intraneural hemorrhage
Tumors
Trauma

*Lesions of the Third Nerve in the Region of the Midbrain*

Nuclear lesions
(*a*) Acute infections: encephalitis, polioencephalitis, botulism, mushroom poisoning
(*b*) Wernicke's polioencephalitis superior
(*c*) Vascular: diabetes; arteriosclerosis
(*d*) Tumors of the midbrain, pons and about the third ventricle
(*e*) Intoxications: lead, carbon monoxide, barbiturates
(*f*) Progressive muscular atrophy
(*g*) Chronic progressive ophthalmoplegia (von Graefe's disease)
(*h*) Gerlier's disease or kubisagari
(*i*) Aphasia
Benedict's syndrome
Weber's syndrome

*Supranuclear Lesions Affecting the Third Nerve*

Cortical lesions: paralytic, irritative
Pontile: paralysis of lateral gaze with preservation of convergence
Midbrain
(*a*) Paralysis of upward movements (Parinaud's)
(*b*) Paralysis of downward movements
(*c*) Paralysis of convergence
(*d*) Vertical nystagmus

*Disorders of the Third Nerve: Miscellaneous Types*

Pupillary abnormalities
- (*a*) Unilateral fixed, dilated pupil associated with expanding cerebral lesions
- (*b*) Argyll Robertson pupil: syphilis, alcoholism, encephalitis, tumors in or about the midbrain, diabetes, multiple sclerosis and trauma
- (*c*) Adie's syndrome
- (*d*) Other pupillary changes

Neuritis: diphtheritic and other systemic infections; "rheumatic" disease; serum treatment

Arteriosclerosis and diabetes

Migrainous ophthalmoplegia

Periodic oculomotor paralysis: familial types

DISCUSSION

DR. ROBERT A. GROFF: From the surgical standpoint, I have been interested in the third nerve in connection with meningioma of the sphenoid ridge. I have seen about 4 cases of complete paralysis of the third nerve associated with meningioma of the lesser wing of the sphenoid ridge. In the case mentioned by Dr. Adler, the diagnosis was apparently made early, and he is to be congratulated on this. In the cases in which there was complete palsy of the third nerve, even though the tumor was completely removed, there was no recovery. I have also seen cases of pontile glioma and pinealoma causing paralysis of upward or lateral gaze, which is the result of impairment of the third nerve. I have been interested in the dilatation of the pupil occurring in association with subdural hematoma. In a series of over 50 cases, I have seen 12 in which the pupil was dilated; in 6 of these cases it occurred on the same side as the hematoma and in 6 on the opposite side; this particular sign does not seem to have much value in localization.

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## CHICAGO NEUROLOGICAL SOCIETY

HARRY PASKIND, M.D., *President, in the Chair*

*Regular Meeting, Feb. 20, 1941*

**Meningioma of the Falx: Report of a Case.** DR. ADRIEN VERBRUGGHEN.

A man aged 50 was admitted to the Michael Reese Hospital with a swelling of the forehead at the hair line and a history of many fainting spells. When he was a small boy he fell and injured his head. When he was 21 years of age he noticed a swelling in the upper part of his forehead which, he said, corresponded to the site of the injury as a boy. During the last thirty-seven years the swelling had become gradually larger. In the last two years he had had increasingly frequent seizures of a generalized character, combined with severe headaches.

Neurologic examination showed some spasticity and weakness of the right side of the body. There was a Babinski sign on the right, but no sensory disturbances. Slight weakness was noted in the left leg. The cranial nerves appeared to be normal. The fundi showed nothing abnormal.

The patient had a large hyperostosing parasagittal meningioma. The principal reason for making this report is the large size of the tumor, which, with the bone removed, weighed 194 Gm. The tumor was calcified and was easily seen in the roentgenogram. It occupied a large part of the cranial cavity. It was removed in two stages, four days apart. At the first stage the bone was removed from the overlying tumor, and at the second stage the dura was incised on both sides

over the cavity of the hemispheres, the falx was ligated in front of and behind the tumor and the entire mass removed.

The patient made an uneventful recovery, and the question now arises whether anything should be done about the large bony deformity. The right side is still somewhat weak and spastic. The euphoria and peculiarities of behavior have been eliminated, and from a social point of view he is now able to care for himself.

DISCUSSION

DR. PETER BASSOE: I should like to ask Dr. Verbrugghen whether the bone which was removed was decalcified and sections made, and whether any tumor was found in the bone.

DR. ROY GRINKER: Mention should have been made of the minimal amount of neurologic disability this man had after so many years of pressure. Perhaps that could be accounted for by the slow growth of the tumor and the adaptation of the tissue. Evidences of paraplegia and bladder symptoms developed only lately. The clinical picture was entirely out of proportion to the size of the mass.

I had recommended surgical intervention, not with any hope of improving the patient's disabilities but with the idea of preventing further damage.

DR. ADRIEN VERBRUGGHEN: In reply to Dr. Bassoe's question, I do not think the bone was sectioned. It was not decalcified.

**Vibration Sensibility in the Face Following Retrogasserian Neurectomy.**

DR. MEYER BROWN and (by invitation) DR. GEORGE YACORZYNSKI.

Vibration sensibility in the face was studied in 9 patients who had been subjected to unilateral retrogasserian neurectomy. Thresholds at frequencies of 100 double vibrations per second were ascertained for five different points on each side of the face and tongue, and the upper limit of frequency of vibration perceived was determined at these points under the limitations imposed by our apparatus. We found that the loss of tactile sensibility in the face produced by section of the trigeminal root is associated with diminution in vibratory sensibility in the lips and tongue. In the forehead and cheek vibrations delivered by our apparatus under the conditions of the present experiment could not be perceived except in 2 instances.

It is suggested that the perception of vibrating stimuli in the face depends on the stimulation of both touch and deep pressure receptors. Vibration sensibility, therefore, is to be regarded as the apperception of repetitive mechanical stimuli delivered to either deep or superficial receptors or to both varieties of end organs. The type of apparatus used, the manner in which it is used and the innervation of the area stimulated determine the relative importance of pressure or tactile end organs in the perception of vibration.

DISCUSSION

DR. PERCIVAL BAILEY: How do the authors explain the 2 exceptions found in examination of the forehead and cheek? Did the surgeon perhaps miss some fibers?

DR. ADRIEN VERBRUGGHEN: Is there any information about the motor roots in these cases? Did I understand correctly that 1 patient was operated on twenty years ago?

DR. R. P. MACKAY: There is some doubt whether the sensation studied by the authors is the same as that measured by placing the base of a vibrating tuning fork on the bony prominence of the internal malleolus. To place the free end of a vibrating stylus lightly on the skin over soft tissue can scarcely test the same function as to press heavily with the base of a fork on a bony prominence and so set the whole bone into vibration. In the first instance, tactile sensibility must be involved more than any other; in the second, some other

sense than the tactile is stimulated. In my opinion, the two forms of sensation are entirely different.

DR. MEYER BROWN: In response to Dr. Bailey's question, I must say that I have no explanation for the 2 exceptions to the 18 observations which dealt with the perception of vibrating stimuli in the forehead and cheek after section of the trigeminal nerve root. It may be remembered that in the 4 instances out of 22 in which vibrations were not felt in the anesthetic lips, the thresholds for these areas on the side opposite that of operation were also unusually high.

We did not anesthetize the normal skin while examining the face on the side of operation because, as we have shown, the spread of vibration from one side of the face to the opposite side was so slight that it has no significance in the present study.

Stimulation by the vibrating point was established by mere contact between it and the skin; pressure sufficient to deform the surface of the skin was scrupulously avoided.

Dr. Mackay has raised an interesting point when he compares the sensation produced by a vibrating tuning fork placed on the crest of the tibia with the sensations evoked by our vibrating stimulus. In either case one is dealing with repetitive mechanical impacts, but the weight of the vibrating object, its amplitude of excursion and the pressure it exerts against the stimulated surface are so different that perception of subjectively different sensations is a reasonable observation. It is our belief that this difference in stimulus as well as in its mode of application causes sense organs of different types to be activated to varying degrees and in varying numbers. Thus, a light vibrating point barely touched to the skin brings the immediate subadjacent tactile receptors into play to a larger extent than receptors of fascia, muscle or periosteum, while the base of a heavy tuning fork pressed against the tibia probably stimulates pressure receptors of bone and connective tissue over a wide area more than it does the tactile end organs. It is of most significance to realize that a subjective sense of vibration may be elicited by means of mechanical repetitive stimuli to either tactile or deep receptors in large or small numbers, depending on the methods and instruments used for examination.

DR. GEORGE YACORZYNSKI: I want to elaborate on the last question because of its practical and theoretic implications. We believe that the clinical method of applying the base of a tuning fork to the skin to measure the vibratory sensitivity and the procedure which we used involve the same perceptual mechanisms. The difference which is found between the vibratory threshold when the base of a tuning fork and that when some other apparatus is applied to the skin can be accounted for on the basis of the differences of amplitude of the stimulators. The amplitude of vibration of the base of a fork would be small as compared, for example, with the amplitude of the prongs of the tuning fork or with the apparatus which we used. Since, with other conditions constant, the sensation of vibration is a function of both the amplitude and the frequency of the stimulator, one would expect that the base of the tuning fork applied on certain parts of the body, such as the cheek, would elicit no perception of vibration. If the amplitude of vibration was increased, as is possible with the apparatus we used, the perceptual response could be elicited.

**Intracranial Chordoma.** DR. HOWARD ZEITLIN and (by invitation) DR. S. A. LEVINSON.

This article was published in full in the June 1941 issue of the ARCHIVES, page 984.

DISCUSSION

DR. ARTHUR WEIL: I should like to ask whether specimens of the tumor had been taken for biopsy and whether there were any changes in the histologic structure of the tumor. Davison and I reported a case (Malignant Chordoma

of the Lumbar Region, ARCH. NEUROL. & PSYCHIAT. **19**:415 [March] 1928) in which operation had been performed six months before and we were fortunate enough to have for study both the primary biopsy specimen and the autopsy material. At operation the typical picture of a chordoma, with the large "physaliphorous" cells, was found. But six months later the tumor had assumed a malignant, sarcoma-like appearance and had invaded the surrounded bony structures.

DR. PERCIVAL BAILEY: I should like to ask whether the clivus was examined for the presence of any similar tissue.

DR. JOHN MARTIN: To emphasize the statement of the authors that these tumors are rare, I should like to mention that in our series of approximately 670 verified intracranial tumors, my associates and I have seen but 1 chordoma. This was in a man aged 45 whose major complaint was that of epileptiform seizures. He was in poor condition when he was eventually sent to us for surgical treatment. At operation an enormous tumor was seen pushing from under the brain to the right and displacing the temporal lobe. Approximately 2 ounces (56 Gm.) of pale pinkish tissue, very soft and watery, was removed. The patient died the following day, and at autopsy the tumor was found to arise from the clivus, and measured more than 6 cm. in its greatest diameter. Histologically it resembled Dr. Zeitlin's third section, the third, or final, stage in the development of a chordoma.

DR. HOWARD ZEITLIN: In answer to Dr. Weil's question: The specimen for biopsy was very small, and its point of removal could not be detected on the surface of the large tumor mass removed at autopsy. Microscopically no sarcomatous changes were evident.

In answer to Dr. Bailey: In the autopsy records the clivus was described as roughened and pitted. As the diagnosis of chordoma was not suspected at the time the autopsy was performed, I doubt whether the clivus was split down the center for the possible evidence of notochord tissue.

**Biochemical Disturbances Associated with Mental Disorders: 1. The Anti-Insulin Effect of the Blood in Schizophrenia.** DR. L. J. MEDUNA, DR. F. J. GERTY and (by invitation) DR. V. G. URSE.

DISCUSSION

DR. S. H. KRAINES: Some time ago Dr. Meduna mentioned the work he was doing, and I told him of the similar experiments I had started in 1938. The striking similarity of our results (although we conducted the experiments without each other's knowledge) is interesting proof of their validity. My work has not yet been published. I used essentially the same technic as did these authors, although I used insulin in proportion to the weight of the rabbit, 0.5 unit per kilogram. Moreover I used only 2 cc. of human serum. It is interesting that the drop in blood sugar, inhibited by the mixture of insulin with 2 cc. of serum, was almost as great as the authors obtained with 20 cc. of whole blood.

I tested the same rabbit a number of times. Using 1 rabbit and repeating the tests on this animal with serum from different persons, I obtained the same results. Moreover, I injected blood on one side intraperitoneally and the insulin subcutaneously, and the same inhibitory effect was obtained; so the effect is due not to the mixture but to something in the patient's blood. The results, however, are expressed in averages. If one studies the curve of the individual patient's blood, one finds there are such extreme variations from person to person that it is impossible to use the test diagnostically for any patient. Occasionally the serum of a schizophrenic patient did not show this inhibitory effect. Not only that, but the day to day blood of the same patient had different effects on the rabbit. I note these points to show the complexity of the study. Never-

theless, it is obvious that there is something in the blood of the "average" schizophrenic patient which inhibits the action of insulin.

DR. RICHARD B. RICHTER: Had any of the patients in these experiments previously been treated with insulin to induce shock?

DR. EARL WALKER: I should like to inquire whether there can be established a correlation between the clinical type of schizophrenia and the amount of anti-insulin substance present in the blood. It seems possible that the mental status of the patient and his physical condition might play a role in the results which have just been reported. Conceivably, the dextrose metabolism of the patient who was in an excited phase might differ distinctly from that of the chronic, deteriorated, mute schizophrenic patient. I believe that the insulin tolerance curve of the schizophrenic patient would be of considerable value in determining the presence of anti-insulin substance in the blood. I wonder if this was determined for any of these patients.

DR. HARRY PASKIND: I should like to ask whether the differences noted in the various groups were constant from patient to patient and from animal to animal and whether critical ratios of the differences were calculated mathematically. If not, how has the mathematical validity of the statistical differences been established? It would be interesting if on calculation a critical ratio of 2 or 2.5 or over were found.

DR. L. J. MEDUNA: One's first question is, What is learned about schizophrenia from our test? This test indicates that a certain group of patients with mental disease are characterized by a disturbance of carbohydrate metabolism. This disturbance manifests itself by the presence of an inhibitory factor. About 60 per cent of the schizophrenic patients are included in this group.

Our test also explains the occasional strange reaction of schizophrenic patients during insulin therapy. In this connection I should like to call attention to Dr. Banting's work published in the *American Journal of Psychiatry* (**95**:562, 1938). He examined a patient who during insulin therapy became resistant to the drug, so that even 1,000 units failed to produce coma. In this particular case a mouse test showed an increase of the anti-insulin factor in the patient's blood. Dr. Banting attributed this anti-insulin factor to the previous insulin therapy. But all our patients were untreated prior to the test, a factor which proves that the disturbance described is one of the pathogenic features of schizophrenia.

I should mention some necessary technicalities. The individual variations of the animals are great; therefore in making the test every one must work out his own standards. Each animal must be used only once for the test. The blood of the patients must be taken in the morning as early as possible to avoid the possible influence of daytime activities or of any other excitement.

Our average curves express the mathematical mean only, but I should like to emphasize that more than 50 per cent of cases fall within the average.

We used both commercial solutions of insulin and crystalline insulin. We did not wish to complicate the picture by infusion of sugar into the animals. It must be kept in mind that what is seen is not the reaction of the patient but the reaction of a test animal to some unknown disturbance which one has introduced.

We hope that our investigations, if carried out on a large scale, will provide such standards that this test may become routine.

# Book Reviews

**Comparative Psychology of Mental Development.** By Heinz Werner. Translated by E. B. Garside. Price $4. Pp. XII + 510. New York: Harper & Brothers, 1940.

Although this is actually the third edition of Werner's book, it is the first English translation. The author's chief object is to demonstrate the similarities in mental processes of various groups throughout the biologic world, specifically animals, children, psychotic persons and primitive peoples. He emphasizes this similarity, while recognizing that "there is a qualitative difference between the thinking of primitives and the level of thought of the intellectual man of western civilization." He is also aware of the fact that the mechanism of thought of children varies from that of primitive man in a particular and material sense, while possessing a similar mental structure in a general and purely formal sense. With these exceptions, however, Werner emphasizes throughout his book the basic similarities of these groups without further indication of their differences.

His studies of child psychology, from the developmental point of view, are complete and leave little to be desired, although he perhaps overemphasizes the primitive-like behavior of children.

Drawing in a general fashion from a vast anthropologic literature, Werner attempts to prove the concreteness of thought and the lack of abstract behavior among primitive persons. While the numerous examples substantiating his points are well chosen, they provide illustrations, not demonstrations. There is insufficient consideration of instances which do not support his concepts. Other workers in the field, such as Radin, have presented equally important discussions to indicate the philosophic nature and capacity for abstract thought of primitive man.

In presenting instances of psychopathologic behavior, the author's lack of differentiation in this field detracts tremendously from the value of his observations. He uses the terms "psychopathic" and "psychotic" interchangeably, and indiscriminately selects examples from cases of schizophrenia, injury to the brain and cerebral tumor to prove his points. He lumps all of these various psychopathic types under the term "psychotic" and shows little consideration for current American nosologic groupings, or even for clinical taxonomic evaluations.

In view of the fact that most anthropologists do not accept the theory of a basic similarity in the mental productions of schizophrenic patients, children and savages and that many psychiatrists believe that such similarities are merely phenomenologic, Werner's book, containing as it does many dogmatic statements, is likely to be productive of considerable controversy.

On the other hand, Werner's studies on synesthesia, experimental behavior in children and the syncretic nature of schizophrenic thinking, together with his general theories, are important to all students in the fields of psychopathology, anthropology or child psychology. It is unfortunate that the book lacks sufficient cohesion to bring the great mass of accumulated facts together in compact form, but in spite of this drawback the data are of considerable value. The work as a whole should be provocative of thought and do much to awaken interest in problems of comparative mental development.

**A Textbook of Clinical Neurology.** By J. M. Nielsen. Price, $6.50. Pp. 672, with 179 illustrations. New York: Paul B. Hoeber, Inc., 1941.

This new textbook contains much that is interesting, but it falls short of what might have been expected of the author from his other writings. It is addressed to students and practitioners and goes into such familiar matters as the distribution of the trigeminal nerve and the technic of lumbar puncture, yet, on the other hand, refers to the theory of neurobiotaxis as common knowledge and presents an extremely complete and complicated differentiation of various types of apraxia.

The book is arranged largely on an anatomic basis. This gives rise to some duplications; thus, causalgia is described under mononeuritis and again under diseases of the sympathetic system. In neither place is much said about treatment. The subject of herpes zoster is similarly doubly represented. Meningitis is described under hydrodynamics and again under infections. Subacute combined degeneration is considered under diseases of the spinal cord, but pernicious anemia and pellagra come under deficiency diseases. Torticollis is mentioned under the diseases of the spinal accessory nerve and viewed purely as a neurosis.

Many important subjects are passed over rather lightly. Thus, while an excellent list of causes of sciatica is given, no concrete outline of differential diagnosis is suggested. Examination of the spinal fluid is mentioned in relation to a few diseases only, and then casually and without quantitative data. The diseases of the optic nerve are presented in a confusing fashion, and the section on visual fields would be obscure to a student. Electroencephalography is mentioned, but briefly and rather disparagingly. In general, pathologic processes are poorly described. The bibliography is spotty.

To turn to the assets of the book, the chapters on the syndromes of the medulla and on cerebral localization are excellent. A long chapter is devoted to the subject of trauma. There is a clear, though rather uncritical, chapter on avitaminoses. An excellent innovation is an enlightened section on addiction. The author writes in a clear and vigorous style, and is at his best when standing firmly on the basis of his own experience.

**Notes on Diffuse Sclerosis, Diffuse Gliomatosis and Diffuse Glioblastomatosis of the Brain, with a Report of Two Cases.** By Einarson and A. Neel. Price, 2.50 Danish kroner. Pp. 56, with illustrations. Copenhagen: Ejnar Munksgaard, 1940.

This brief monograph consists of the reports of 2 cases. The first case is one of a true neoplastic tumor (diffuse glioblastoma), the blastomatous growth constituting the primary phase and the demyelination and the axonal lesions the secondary phase in the process. The localization of the tumor and its spread along blood vessels and fiber tracts are unusual.

The second case is one in which the demyelination is primary and the glial overgrowth secondary, possibly representing an intermediate process between gliosis and the formation of a diffuse astrocytoma.

Several similar cases from the literature are cited and reviewed briefly. The not infrequent occurrence of diffuse gliomas with corresponding demyelination is pointed out.

**Introduction to Psychobiology and Psychiatry.** By Esther L. Richards. Price, $2.50. Pp. 353. St. Louis: C. V. Mosby Company, 1941.

This little book was written for nurses taking training in psychiatric institutions. As the title indicates, psychology and psychiatry are presented from the point of view of Adolf Meyer, whose terminology is used throughout.

The book is admirably suited to its purpose, and shows a deep appreciation of the nurse's problems and point of view. It is further a volume which may prove useful to many medical students, and even neuropsychiatrists, for it is the simplest and clearest statement of the framework of the psychobiologic system of psychiatry that this reviewer has seen. As a corollary, its usefulness as a textbook for nurses would be seriously limited in institutions in which the distinctive terminology is not employed.

The volume is in an inexpensive textbook format, and is not illustrated.

**The Therapy of the Neuroses and Psychoses: A Sociopsychobiologic Analysis and Resynthesis.** By Samuel H. Kraines, M.D. Price $5.50. Pp. 456. Philadelphia: Lea & Febiger, 1941.

"This volume is intended to state as clearly as possible the factors underlying the formation of nervous and mental diseases and their treatment. It is believed that physicians other than psychiatrists will be able to make practical and valuable

application of the principles of therapy herein discussed." These two sentences from the preface express clearly the aims of the book, which are admirably attained.

The first five chapters are devoted chiefly to definitions and descriptions, for the most part objective, concise and informative. Complicated technical terms are studiously avoided. Illuminating examples are given at every turn. Next, psychologic mechanisms are discussed. The simpler psychotherapeutic procedures, such as broad analysis of mechanisms, retraining, attitude therapy, suggestion, hypnosis and drugs, are dealt with in an objective and common sense manner, which could scarcely give offense to adherents of any school of psychiatric thought, or of none. "Psychosomatic" disturbances are well described.

It is of interest that psychoanalytic concepts are freely and adeptly used throughout the book, but the author is critical of organized psychoanalysis. He writes:

> "Cures are not more commonly obtained by psychoanalysis than by eclectic psychiatrists, and what cures are achieved through the psychoanalytic technique of treatment occur because its therapeutic value lies not in its elaborate and questionable superstructure of concepts but rather in four very simple elements. In the first place, the patient finds in the analyst a sympathetic, non-critical listener. In itself, being able to talk freely, without fear of condemnation, serves to release tension. In the second place, the patient discusses his disturbing and distressing attitudes at such length and in such detail that he becomes desensitized to them. Third, through such discussion, moreover, he learns to view his problems objectively, to lose his sense of guilt or self-blame. Finally, he comes to realize that his symptoms have little significance other than as the expression of underlying emotional problems; the understanding of the fact of an emotional basis is helpful, even though theories about this fact may be erroneous.
>
> "These same goals can be achieved far more simply and directly by the therapy as advanced elsewhere in this book, and with the added advantage that not only is the patient taught thereby to understand and be tolerant of his various immature reaction patterns and 'complexes,' but also he is given a technique for actually meeting and solving problems as they arise. Moreover, the mental hygiene concepts advanced in our previous chapters are so inculcated into the patient that they become automatic reaction patterns and not merely intellectually appreciated theories."

The shortcomings of the presentation are perhaps inherent in its assets. In a praiseworthy attempt to remove the mysticism from psychotherapy, the author tends to oversimplify it. The aura of optimism is sometimes overdone. Little is said about the essential qualifications of the psychotherapeutist himself — the necessity for a degree of disinterestedness and openmindedness which is often attained only by special training. On the whole, however, the book is so well adapted to its stated purpose that criticism of small details and debatable overtones is superfluous.